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Attorneys For Plaintiff
Savient Pharmaceuticals, Inc.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

SAVIENT PHARMACEUTICALS, INC. Plaintiff, v. BARR LABORATORIES, INC., Defendant.	Civil Action No. _____

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff, Savient Pharmaceuticals, Inc. ("Savient"), for its complaint against Defendant Barr Laboratories, Inc. ("Barr") alleges as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement that arises under the United States Patent Laws, 35 U.S.C. §§ 100 *et seq.* This action relates to an Abbreviated New Drug Application ("ANDA") filed by Barr with the United States Food and Drug Administration ("FDA") for the approval to market generic versions of Savient's Oxandrin® drug products.

PARTIES

2. Plaintiff Savient is a corporation organized under the laws of the State of Delaware, having its principal place of business at One Tower Center, Fourteenth Floor, East Brunswick, New Jersey 08816.

3. On information and belief, Defendant Barr is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 2 Quaker Road, Pomona, New York 10970-0519.

4. On information and belief, Barr has regular and established places of business at 400 Chestnut Ridge Road, Woodcliff Lake, New Jersey 07677; 109 Morgan Lane, Plainsboro, New Jersey 08536; and 265 Livingston Street, Northvale, New Jersey 07647. On information and belief, Barr is registered to do business in New Jersey.

JURISDICTION AND VENUE

5. This Court has jurisdiction over the subject matter under 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202. Venue is proper in this Court under 28 U.S.C. §§ 1391(b), 1391(c), and 1400(b).

THE PATENTS

6. On February 16, 1999, United States Patent No. 5,872,147, entitled "Use of Oxandrolone in the Treatment of Chronic Obstructive Pulmonary Disease" ("the '147

Patent"), duly and legally issued from the U.S. Patent Office and was subsequently assigned to Savient. A copy of the '147 Patent is attached as Exhibit A.

7. On July 18, 2000, United States Patent No. 6,090,799, entitled "Method for Ameliorating Muscle Weakness/Wasting in a Patient Infected with Human Immunodeficiency Virus-Type 1" ("the '799 Patent"), duly and legally issued from the U.S. Patent Office and was subsequently assigned to Savient. A copy of the '799 Patent is attached as Exhibit B.

8. On June 10, 2003, United States Patent No. 6,576,659, entitled "Use of Oxandrolone in the Treatment of Burns and Other Wounds" ("the '659 Patent"), duly and legally issued from the U.S. Patent Office and was subsequently assigned to Savient. A copy of the '659 Patent is attached as Exhibit C.

9. On December 30, 2003, United States Patent No. 6,670,351, entitled "Method for Ameliorating Muscle Weakness/Wasting in a Patient Infected with Human Immunodeficiency Virus-Type 1" ("the '351 Patent"), duly and legally issued from the U.S. Patent Office and was subsequently assigned to Savient. A copy of the '351 Patent is attached as Exhibit D.

10. On December 7, 2004, United States Patent No. 6,828,313, entitled "Use of Oxandrolone in the Treatment of Burns and Other Wounds" ("the '313 Patent"), duly and legally issued from the U.S. Patent Office and was subsequently assigned to Savient. A copy of the '313 Patent is attached as Exhibit E.

11. At all time from the issuance of the '147, '799, '659, '351, and '313 patents (collectively "the Patents"), Savient or one of its predecessors in interest has been the lawful owner of all rights, title and interest in and to the Patents, including the right to bring

actions and recover damages for infringements thereof. As set forth below, Barr's actions constitute direct infringement, inducement of infringement and contributory infringement of the '147, '799, '659, '351 and '313 Patents in violation of 35 U.S.C. § 271(b), (c) and (e)(2).

FIRST COUNT
(Infringement of the '147 Patent)

12. Savient is the approved holder of NDA 13-718 for 2.5 mg and 10 mg oxandrolone tablets. Savient sells 2.5 mg and 10 mg tablets of oxandrolone under the brand name Oxandrin®.

13. The '147 Patent relates to the administration of oxandrolone to treat patients with chronic obstructive pulmonary disease or adult respiratory distress syndrome.

14. On or about August 14, 2006, Savient received notice (the "Paragraph IV Notice") of Barr's ANDA submission pursuant to Section 505(j)(2)(B) of the Federal Food, Drug and Cosmetic Act (21 CFR § 314.95(c)) requesting FDA marketing approval to manufacture, use or sell 2.5 mg and 10 mg oxandrolone tablets prior to the expiration of the Patents, including the '147 Patent. Barr's ANDA has been assigned number 78-344 by the FDA.

15. On information and belief, Barr's generic oxandrolone tablets, if approved by the FDA, will be administered to practice the method recited by one or more claims of the '147 Patent. Further, such use of oxandrolone tablets will result in direct infringement of the '147 Patent.

16. On information and belief, this infringing use of generic oxandrolone tablets under the '147 Patent will occur at Barr's active behest, and with its intent, knowledge and encouragement, and Barr will actively induce, encourage, contribute to, aid and abet this administration with knowledge that it is in contravention of Savient's rights under the '147 Patent.

17. As a result, by filing its ANDA and requesting FDA marketing approval for a generic copy of Savient's Oxandrin® brand of oxandrolone tablets prior to the expiration of the Patents, including the '147 Patent, Barr will directly and indirectly infringe the claims of the '147 Patent by direct infringement, inducement of infringement and contributory infringement under 35 U.S.C. §§ 271(b), (c), and (e)(2). Savient has been damaged by Barr's infringement and will suffer additional and irreparable damages unless this Court enjoins Barr from continuing its infringement pursuant to 35 U.S.C. § 283.

18. Barr's allegations in its Paragraph IV Notice that the Patents, including the '147 Patent, are invalid, unenforceable or not infringed by Barr's proposed commercial manufacture, use or sale of oxandrolone tablets are factually and legally insufficient. On information and belief, Barr's infringement of the '147 Patent is willful, entitling Savient to an assessment of treble damages pursuant to 35 U.S.C. § 284.

SECOND COUNT
(Infringement of the '799 Patent)

19. Savient repeats and incorporates by reference, as if fully set forth herein, the allegations contained in paragraphs 1 through 18 above.

20. The '799 Patent relates to the administration of oxandrolone to ameliorate HIV-associated myopathy and muscle weakness in AIDS patients.

21. On information and belief, Barr's generic oxandrolone tablets, if approved by the FDA, will be administered to practice the method recited by one or more claims of the '799 Patent. Further, such use of oxandrolone tablets will result in direct infringement of the '799 Patent.

22. On information and belief, this infringing use of generic oxandrolone tablets under the '799 Patent will occur at Barr's active behest, and with its intent, knowledge

and encouragement, and Barr will actively induce, encourage, contribute to, aid and abet this administration with knowledge that it is in contravention of Savient's rights under the '799 Patent.

23. As a result, by filing its ANDA and requesting FDA marketing approval for a generic copy of Savient's Oxandrin® brand of oxandrolone tablets prior to the expiration of the Patents, including the '799 Patent, Barr will directly and indirectly infringe the claims of the '799 Patent by direct infringement, inducement of infringement and contributory infringement under 35 U.S.C. §§ 271(b), (c), and (e)(2). Savient has been damaged by Barr's infringement and will suffer additional and irreparable damages unless this Court enjoins Barr from continuing its infringement pursuant to 35 U.S.C. § 283.

24. Barr's allegations in its Paragraph IV Notice that the Patents, including the '799 Patent, are invalid, unenforceable or not infringed by Barr's proposed commercial manufacture, use or sale of oxandrolone tablets are factually and legally insufficient. On information and belief, Barr's infringement of the '799 Patent is willful, entitling Savient to an assessment of treble damages pursuant to 35 U.S.C. § 284.

THIRD COUNT
(Infringement of the '659 Patent)

25. Savient repeats and incorporates by reference, as if fully set forth herein, the allegations contained in paragraphs 1 through 24 above.

26. The '659 Patent relates to the administration of oxandrolone to treat patients with skin wounds and burns.

27. On information and belief, Barr's generic oxandrolone tablets, if approved by the FDA, will be administered to practice the method recited by one or more claims of the

'659 Patent. Further, such use of oxandrolone tablets will result in direct infringement of the '659 Patent.

28. On information and belief, this infringing use of generic oxandrolone tablets under the '659 Patent will occur at Barr's active behest, and with its intent, knowledge and encouragement, and Barr will actively induce, encourage, contribute to, aid and abet this administration with knowledge that it is in contravention of Savient's rights under the '659 Patent.

29. As a result, by filing its ANDA and requesting FDA marketing approval for a generic copy of Savient's Oxandrin® brand of oxandrolone tablets prior to the expiration of the Patents, including the '659 Patent, Barr will directly and indirectly infringe the claims of the '659 Patent by direct infringement, inducement of infringement and contributory infringement under 35 U.S.C. §§ 271(b), (c), and (e)(2). Savient has been damaged by Barr's infringement and will suffer additional and irreparable damages unless this Court enjoins Barr from continuing its infringement pursuant to 35 U.S.C. § 283.

30. Barr's allegations in its Paragraph IV Notice that the Patents, including the '659 Patent, are invalid, unenforceable or not infringed by Barr's proposed commercial manufacture, use or sale of oxandrolone tablets are factually and legally insufficient. On information and belief, Barr's infringement of the '659 Patent and is willful, entitling Savient to an assessment of treble damages pursuant to 35 U.S.C. § 284.

FOURTH COUNT
(Infringement of the '351 Patent)

31. Savient repeats and incorporates by reference, as if fully set forth herein, the allegations contained in paragraphs 1 through 30 above.

32. The '351 Patent relates to the administration of oxandrolone to ameliorate HIV-associated myopathy and muscle weakness in AIDS patients.

33. On information and belief, Barr's generic oxandrolone tablets, if approved by the FDA, will be administered to practice the methods recited by one or more claims of the '351 Patent. Further, such use of oxandrolone tablets will result in direct infringement of the '351 Patent.

34. On information and belief, this infringing use of generic oxandrolone tablets under the '351 Patent will occur at Barr's active behest, and with its intent, knowledge and encouragement, and Barr will actively induce, encourage, contribute to, aid and abet this administration with knowledge that it is in contravention of Savient's rights under the '351 Patent.

35. As a result, by filing its ANDA and requesting FDA marketing approval for a generic copy of Savient's Oxandrin® brand of oxandrolone tablets prior to the expiration of the Patents, including the '351 Patent, Barr will directly and indirectly infringe the claims of the '351 Patent by direct, inducement and contributory infringement under 35 U.S.C. §§ 271(b), (c), and (e)(2). Savient has been damaged by Barr's infringement and will suffer additional and irreparable damages unless this Court enjoins Barr from continuing its infringement pursuant to 35 U.S.C. § 283.

36. Barr's allegations in its Paragraph IV Notice that the Patents, including the '351 Patent, are invalid, unenforceable or not infringed by Barr's proposed commercial manufacture, use or sale of oxandrolone tablets are factually and legally insufficient. On information and belief, Barr's infringement of the '351 Patent and is willful, entitling Savient to an assessment of treble damages pursuant to 35 U.S.C. § 284.

FIFTH COUNT
(Infringement of the '313 Patent)

37. Savient repeats and incorporates by reference, as if fully set forth herein, the allegations contained in paragraphs 1 through 36 above.

38. The '313 Patent relates to the administration of oxandrolone to increase the rate of healing of skin wounds and to increase the rate of weight gain after burn induced weight loss.

39. On information and belief, Barr's generic oxandrolone tablets, if approved by the FDA, will be administered to practice the method recited by one or more claims of the '313 Patent. Further, such use of oxandrolone tablets will result in direct infringement of the '313 Patent.

40. On information and belief, this infringing use of generic oxandrolone tablets under the '313 Patent will occur at Barr's active behest, and with its intent, knowledge and encouragement, and Barr will actively induce, encourage, contribute to, aid and abet this administration with knowledge that it is in contravention of Savient's rights under the '313 Patent.

41. As a result, by filing its ANDA and requesting FDA marketing approval for a generic copy of Savient's Oxandrin® brand of oxandrolone tablets prior to the expiration of the Patents, including the '313 Patent, Barr will directly and indirectly infringe the claims of the '313 Patent by direct infringement, inducement of infringement and contributory infringement under 35 U.S.C. §§ 271(b), (c), and (e)(2). Savient has been damaged by Barr's infringement and will suffer additional and irreparable damages unless this Court enjoins Barr from continuing its infringement pursuant to 35 U.S.C. § 283.

42. Barr's allegations in its Paragraph IV Notice that the Patents, including the '313 Patent, are invalid, unenforceable or not infringed by Barr's proposed commercial manufacture, use or sale of oxandrolone tablets are factually and legally insufficient. On information and belief, Barr's infringement of the '313 Patent and is willful, entitling Savient to an assessment of treble damages pursuant to 35 U.S.C. § 284.

PRAYER FOR RELIEF

WHEREFORE, Savient demands judgment against Barr and respectfully prays that this Court enter orders which:

(a) Preliminarily and permanently enjoin Barr and its officers, agents, employees and all others in concert or participation with it, including without limitation, its parent corporation Barr Pharmaceuticals, Inc. and subsidiaries, from further acts of direct infringement, inducement of infringement, and contributory infringement of the '147, '799, '659, '351 and '313 Patents;

(b) Order that the effective date of any approval of Barr's application under Section 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j), for 2.5 mg and 10 mg tablets of oxandrolone and its manufacture, sale or use be not earlier than the date the last of the Patents expires;

(c) Award to Savient the damages it has sustained by reason of Barr's acts of inducement of infringement and contributory infringement, and the resulting direct infringement, together with pre- and post-judgment interest as allowed by law;

(d) Award to Savient treble the damages assessed pursuant to 35 U.S.C. § 284 by reason of the willful nature of Barr's infringement;

(e) Declare this case to be "exceptional" and award to Savient its reasonable attorneys' fees pursuant to 35 U.S.C. § 285;

(f) Award to Savient its costs and expenses of this action as allowed by law; and

(g) Award to Savient such other and further relief as the Court may deem just and proper.

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Dated: September 26, 2006

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RULE 11.2 CERTIFICATION

I hereby certify that this matter is not the subject of any other action asserted by the Plaintiff herein, in any other action pending in any court or of any pending arbitration.

SAIBER SCHLESINGER SATZ & GOLDSTEIN, LLC
Attorneys for Plaintiff Savient Pharmaceuticals, Inc.

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RULE 201.1 CERTIFICATION

Pursuant to L. Civ. R. 201.1, the undersigned counsel for the Plaintiff hereby certifies that the amount in controversy, excluding interest, costs and punitive damages exceeds $150,000, and that this action is not appropriate for compulsory arbitration.

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Attorneys for Plaintiff Savient Pharmaceuticals, Inc.

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EXHIBIT A

US005872147A

United States Patent [19]

Bowen

[11] Patent Number: 5,872,147

[45] Date of Patent: Feb. 16, 1999

[54] USE OF OXANDROLONE IN THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

[75] Inventor: Robert E. Bowen, Martinsburg, W. Va.

[73] Assignee: Bio-Technology General Corp., Iselin, N.J.

[21] Appl. No.: 986,015

[22] Filed: Dec. 5, 1997

Related U.S. Application Data

[60] Provisional application No. 60/032,107 Dec. 5, 1996.

[51] Int. Cl.[6] A61K 31/335

[52] U.S. Cl. 514/453; 514/174

[58] Field of Search 514/453, 174

[56] References Cited

U.S. PATENT DOCUMENTS

3,128,283	4/1964	Pappo	514/453
4,039,668	8/1977	Fuchs et al.	514/177
4,376,733	3/1983	Frimer	549/268
4,914,106	4/1990	Shibata et al.	514/453
5,096,916	3/1992	Skupin	514/401

OTHER PUBLICATIONS

Desforges, Current Concepts, vol. 328, pp. 1017–1022, 1993.

New England J. of Med., pp. 1017–1021, 1993.

Ann of Intern. Med., vol. 114, pp. 216–223, 1991.

Primary Examiner—James H. Reamer

Attorney, Agent, or Firm—John P. White; Cooper & Dunham LLP

[57] ABSTRACT

The subject invention provides a method of treating a symptom associated with chronic obstructive pulmonary disease in a patient suffering from chronic obstructive pulmonary disease which comprises administering a therapeutically effective amount of an oxandrolone to the patient. The subject invention further provides a method of improving functional capacity and/or pulmonary function in a patient suffering from chronic obstructive pulmonary disease which comprises administering a therapeutically effective amount of an oxandrolone to the patient.

15 Claims, No Drawings

USE OF OXANDROLONE IN THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

This application claims priority of U.S. Provisional application Ser. No. 60/032,107, filed Dec. 5, 1996, the contents of which are hereby incorporated into this application by reference.

Throughout this specification, various publications are referenced by Arabic numerals within parentheses. Full citations for these references may be found at the end of the specification immediately preceding the claims. The disclosure of these publications in their entireties are hereby incorporated by reference into this specification in order to more fully describe the state of the art to which this invention pertains.

BACKGROUND OF THE INVENTION

Chronic Obstructive Pulmonary Disease (COPD)

COPD is a progressively debilitating disease affecting an estimated 16 million Americans. In 1984, COPD ranked fifth as the leading cause of death in the United States. From a disability standpoint, COPD is the most frequent reason that people seek medical attention (1).

It has been found that there is a direct relationship between body weight and respiratory muscle mass (2) and that a significant percentage of patients with COPD are malnourished (1, 2). Epidemiologic surveys of COPD have suggested that undernutrition might be an important prognostic variable (2). When the COPD patient begins to lose weight, the average life expectancy is only 2.9 years (1).

Disabilities in patients with COPD due to limitations in pulmonary function are often compounded by a loss of muscle strength and lean body mass, resulting in an inability to perform many activities of daily living. These losses may be attributable to a number of factors including decreased ability to exercise, decreased appetite, hypermetabolism and protein catabolism resulting from prolonged glucocortoid therapy. Because of undue dyspnea, these patients are frequently afraid to exercise, which exacerbates their muscle wasting condition. Shortness of breath during eating also worsens this condition because it leads to inadequate caloric and protein intake. Furthermore, many of these patients are receiving intermittent or chronic treatment with anti-inflammatory steroids that may result in myopathy, especially causing weakness in the proximal lower extremities. A combination of these factors often contribute to disability in patients with COPD that exceeds what would generally be expected based on airflow limitation alone.

Because of the progressive decline due to dyspnea and cachexia in these patients, levels of morbidity and mortality exceed those expected based on pulmonary limitations alone.

The subject invention provides therapies to reverse or halt the catabolic process and restore lean body mass in COPD patients. The subject invention also provides therapies to improve functional capacity and/or pulmonary function in these patients.

Adult Respiratory Distress Syndrome (ARDS)

ARDS consists of respiratory failure associated with various acute pulmonary injuries and is characterized by noncardiogenic pulmonary edema, respiratory distress and hypoxemia.

ARDS may be caused by a variety of pulmonary or systemic insults but is particularly frequent in patients with sepsis. Although termed "adult", ARDS occurs in children as well as adults.

Oxandrolone

Oxandrolone (17-methyl-17-hydroxy-2-oxa-5-androstan-3-one) is a known compound which is commercially available. The preparation of oxandrolone is described, inter alia, in U.S. Pat. No. 3,128,283. Oxandrolone is an anabolic steroid synthetically derived from testosterone. Oxandrolone has a unique chemical structure compared with other testosterone analogs. Oxandrolone contains an oxygen rather than a carbon atom at the 2-position within the phenanthrene nucleus (3) and lacks a 4-ene function in the A-ring. The anabolic activity of oxandrolone is approximately 6 times greater than its androgenic activity and has been found to be 6.3 times greater than that of methyltestosterone (3).

Anabolic activity refers to the ability to cause nitrogen retention, promoting weight gain and increasing muscle strength. Androgenic activity refers to the ability to enhance male characteristics (i.e. secondary sex characteristics such as facial hairs and voice changes). Because of the high ratio of anabolic to androgenic activity, oxandrolone is less likely to cause adverse cosmetic consequences in women than many testosterone analogs.

Furthermore, in contrast to the majority of oral androgenic anabolic steroids (e.g. micronized testosterone, methyltestosterone, fluoxymesterone), oxandrolone undergoes relatively little hepatic metabolism (4, 5).

Oxandrolone has been administered to malnourished patients with alcoholic hepatitis (6, 7). Oxandrolone has been shown to be safe even in dosages of up to 80 mg/day in patients with alcoholic hepatitis (6).

The subject invention discloses the use of an oxandrolone for the treatment of symptoms associated with chronic obstructive pulmonary disease and symptoms associated with ARDS.

SUMMARY OF THE INVENTION

The subject invention provides a method of treating a symptom associated with chronic obstructive pulmonary disease in a patient suffering from chronic obstructive pulmonary disease which comprises administering a therapeutically effective amount of an oxandrolone to the patient.

The subject invention further provides a method of improving functional capacity and/or pulmonary function in a patient suffering from chronic obstructive pulmonary disease which comprises administering a therapeutically effective amount of an oxandrolone to the patient.

DETAILED DESCRIPTION OF THE INVENTION

Oxandrolone as used herein encompasses 17-methyl-17-hydroxy-2-oxa-5-androstan-3-one (both racemic mixtures and optically active enantiomers) as well as pharmaceutically acceptable esters thereof. For example, an oxandrolone product which is commercially available is the Oxandrin® tablet from BTG Pharmaceuticals Corp., Iselin, N.J. 08830, which is 17α-methyl-17β-hydroxy-2-oxa-5α-androstan-3-one. This product was used throughout the studies described herein.

Oxandrolone may be administered orally, intravenously, intramuscularly, subcutaneously, topically, intratracheally, intrathecally, intraperitoneally, rectally, vaginally or intrapleurally.

If oxandrolone is administered orally, it is administered in the form of a tablet, a pill, a liquid or a capsule.

A liquid may be administered in the form of a solution or a suspension.

The compositions produced in accordance with the invention may comprise conventional pharmaceutically acceptable diluents or carriers. Tablets, pills, liquids and capsules may include conventional excipients such as lactose, starch, cellulose derivatives, hydroxypropyl methylcellulpse and magnesium stearate. Suppositories may include excipients such as waxes and glycerol. Injectable solutions will comprise sterile pyrogen-free media such as saline and may include buffering agents, stabilizing agents, solubilizing agents or preservatives. Conventional enteric coatings may also be used.

Compositions for topical administration may be in the form of creams, ointments, lotions, solutions, transdermal delivery systems, transdermal patches or gels.

The subject invention provides a method of treating a symptom associated with chronic obstructive pulmonary disease in a patient suffering from chronic obstructive pulmonary disease which comprises administering a therapeutically effective amount of an oxandrolone to the patient.

The symptom may inter alia be cachexia, muscle wasting, involuntary weight loss.

The subject invention further provides a method of improving pulmonary function in a patient suffering from chronic obstructive pulmonary disease which comprises administering a therapeutically effective amount of an oxandrolone to the patient.

The subject invention also provides a method of improving functional capacity and/or functional status and/or exercise capacity in a patient suffering from chronic obstructive pulmonary disease which comprises administering a therapeutically effective amount of an oxandrolone to the patient.

Functional capacity may be tested by the ability to carry out the activities of daily living such as walking, doing housework, carrying groceries, and may also be tested by exercise tolerance, ambulatory status, increased energy or increased mobility inter alia. Functional status and/or exercise capacity are tested in the same manner.

The subject invention also provides a use of an oxandrolone in the preparation of a composition to treat a symptom associated with COPD or to improve functional capacity and/or pulmonary function in a patient suffering from COPD.

In a preferred embodiment, the amount of the oxandrolone is about 10–20 mg per day.

In especially preferred embodiments, the amount of the oxandrolone is about 0.2 mg/kg per day.

Oxandrolone may be administered in a solid dosage form, in a liquid dosage form, in a sustained-release formulation or in a once a day formulation. The liquid dosage form may inter alia be alcohol-based or formulated with a cyclodextrin such as hydroxypropyl-β-cyclodextrin.

Interferon as used herein encompasses any interferon such as alpha-interferon, beta-interferon or gamma-interferon.

Corticosteroid as used herein encompasses inter alia glucocorticoids, mineralcorticoids and androgens. Examples of glucocorticoids are hydrocortisone, cortisone, corticosterone and synthetic analogs of hydrocortisone and cortisone (such as cortisol, prednisolone and prednisone). Examples of mineralcorticoids are aldosterone and desoxycorticosterone. Examples of androgens are DHEA, androstenedione, testosterone and 11β-hydroxyandrostenedione.

Oxandrolone may be administered in conjunction with an interferon, a corticosteroid or any known anti-inflammatory agent.

Oxandrolone may also be administered in conjunction with glutamine or human growth hormone.

The subject invention also provides a method of improving functional capacity and/or pulmonary function in a patient suffering from adult respiratory distress syndrome which comprises administering a therapeutically effective amount of an oxandrolone to the patient.

EXAMPLE

The Example which follows is set forth to aid in understanding the invention but is not intended to, and should not be construed to, limit its scope in any way.

The effect of oxandrolone in the treatment in a group of patients with COPD in reversing or stabilizing their progressive decline in pulmonary function, functional capacity and body weight, by increasing lean body mass and proximal muscle strength

A study on the effect of oxandrolone on patients with COPD was performed as follows.

Patient characteristics

Eighteen (18) patients (11 women and 7 men), ranging in age from 47–77 who had a pulmonary function (FEV_1) of less than 50% of predicted normal according to their size and age, were included in this study. Patients served as their own controls. Of the 18 patients enrolled, 17 completed the study. One patient declined to continue participation after carefully reading the consent form and did not receive treatment with oxandrolone. None of the patients stopped taking the drug because of adverse effects.

Study design

17 patients received 0.2 mg/kg/day of oxandrolone in a single dose for 8 weeks. Baseline values were obtained for pulmonary function, percentage of body fat, maximum oxygen consumption (VO_2max) and leg muscle strength. Total cholesterol and HDL levels were also determined as well as SGOT levels. Assessments were repeated at 5 and 10 weeks after treatment was initiated. Thus, the last assessment was 2 weeks after the last dose of oxandrolone.

Testing procedures

Med-Graphics equipment with Breeze software was used to assess pulmonary function. Percentage of body fat was determined by the infrared method using the Futrex 5000 body fat analyzer. VO_2max was evaluated based on a modified Balke protocol with collection of expired gases and breath-by-breath analysis on Med-Graphics metabolic cart. The Nautilus® leg extension machine was used to assess proximal leg muscle strength. Patients were asked to extend their legs bearing their maximum weight for six repetitions. Results were analyzed for statistical significance using the Student's t test.

Results

TABLE 1

effects of 8 weeks of oxandrolone therapy on lean body mass and muscle strength in patients with COPD.

Parameters assessed	Before treatment with oxandrolone (0.2 mg/kg/d)	Follow-up, after Initiation of Oxandrolone Treatment (Week 10)	p value
Body weight (lbs)	125.5	127.1	NS
Body fat	23.5	20.7	<0.001

TABLE 1-continued

effects of 8 weeks of oxandrolone therapy on lean body mass and muscle strength in patients with COPD.

Parameters assessed	Before treatment with oxandrolone (0.2 mg/kg/d)	Follow-up, after Initiation of Oxandrolone Treatment (Week 10)	p value
(%)			
FEV_1	1.07	1.12	<0.01
Proximal leg strength	40.3	58.9	<0.001
Total cholesterol	206 mg/DL	205	NS
HDL	52.2	53.6	NS
VO_2max	18.6 mL/min/m^2	21.8	<0.001
SGOT	32 U/L	32.4	NS

NS = not significant

As can be seen from Table 1, oxandrolone produced significant differences in percentage of body fat, leg extension muscle strength and VO_2max. There was a small insignificant increase in body weight. Body fat, however, was significantly decreased by 3% ($p<0.001$) suggesting an increase in lean body mass consistent with the anabolic effect of oxandrolone. The most significant improvement noted was in leg extension muscle strength. Maximum weight lifted upon leg extension increased from an average of 40.3 pounds to 58.9 pounds ($p<0.001$). Such a significant improvement in muscle strength allows patients greater and more efficient mobility that enables them to accomplish tasks of daily living with less distress.

Surprisingly, VO_2max increased significantly from 18.6 to 21.8 mL/min/m^2 ($p<0.001$). VO_2max is an excellent indicator of an individual's fitness level and quantitates ability to perform daily functions.

Notably, a subgroup of six patients with less severe pulmonary impairment at the onset of the study showed the most improvement. In these patients whose VO_2max exceeded 17 at the onset of the trial, oxandrolone treatment increased VO_2max from 19.4 to 24.2 mL/min/m^2. This may indicate that patients with moderate to severe pulmonary impairment may benefit more from oxandrolone therapy than patients with very severe impairment. At very severe levels of impairment, airflow may limit any improvement in VO_2max regardless of the improvement in proximal muscle strength.

In addition, patients achieved a statistically significant improvement in FEV_1, with values increasing from 1.07 to 1.12 liters ($p<0.01$).

There were no significant differences in total cholesterol, HDL or SGOT levels and there were no reported adverse effects during this study.

The results of this study indicate that oxandrolone is a safe and effective treatment for symptoms associated with COPD.

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What is claimed is:

1. A method of treating a symptom associated with chronic obstructive pulmonary disease in a patient suffering from chronic obstructive pulmonary disease which comprises administering a therapeutically effective amount of an oxandrolone to the patient.

2. A method according to claim **1**, wherein the symptom is cachexia, muscle wasting or involuntary weight loss.

3. A method of improving pulmonary function in a patient suffering from chronic obstructive pulmonary disease which comprises administering a therapeutically effective amount of an oxandrolone to the patient.

4. A method of improving functional capacity in a patient suffering from chronic obstructive pulmonary disease which comprises administering a therapeutically effective amount of an oxandrolone to the patient.

5. A method according to claims **1**, **3**, or **4** wherein the amount of the oxandrolone is about 1–100 mg/day.

6. A method according to claim **5** wherein the amount of the oxandrolone is about 10–20 mg/day.

7. A method according to claim **5** wherein the amount of the oxandrolone is about 0.2 mg/kg/day.

8. A method according to claims **1**, **3** or **4** wherein the oxandrolone is administered orally.

9. A method according to claims **1**, **3**, or **4** wherein the oxandrolone is injected.

10. A method according to claims **1**, **3**, or **4** wherein the oxandrolone is in a solid dosage form.

11. A method according to claims **1**, **3**, or **4** wherein the oxandrolone is in a liquid dosage form.

12. A method according to claims **1**, **3**, or **4** wherein the oxandrolone is in a sustained-release formulation.

13. A method of improving pulmonary function in a patient suffering from adult respiratory distress syndrome which comprises administering a therapeutically effective amount of an oxandrolone to the patient.

14. A method of improving functional capacity in a patient suffering from adult respiratory distress syndrome which comprises administering a therapeutically effective amount of an oxandrolone to the patient.

15. A method according to claims **1**, **3**, **4**, **13** or **14**, wherein the oxandrolone is 17α-methyl-17β-hydroxy-2-oxa-5α-androstan-3-one.

* * * * *

EXHIBIT B

US006090799A

United States Patent [19]

Berger

[11] Patent Number: 6,090,799

[45] Date of Patent: Jul. 18, 2000

[54] METHOD FOR AMELIORATING MUSCLE WEAKNESS/WASTING IN A PATIENT INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS-TYPE 1

[75] Inventor: **Joseph R. Berger**, Miami, Fla.

[73] Assignee: **BTG Pharmaceuticals Corp.**, Iselin, N.J.

[21] Appl. No.: **08/244,988**

[22] PCT Filed: **Oct. 20, 1993**

[86] PCT No.: **PCT/US93/10063**

§ 371 Date: **Jun. 22, 1995**

§ 102(e) Date: **Jun. 22, 1995**

[87] PCT Pub. No.: **WO94/08590**

PCT Pub. Date: **Apr. 28, 1994**

[51] **Int. Cl.**[7] A61K 31/56

[52] **U.S. Cl.** 514/179

[58] **Field of Search** 514/179

[56] **References Cited**

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Primary Examiner—Russell Travers

Attorney, Agent, or Firm—John P. White; Cooper & Dunham LLP

[57] **ABSTRACT**

A method for attenuating the HIV-associated myopathy and muscle wasting associated with infection by human immunodeficiency virus-Type 1. Administration of oxandrolone in a daily dosage of about 2.5 to about 20 milligrams is described.

8 Claims, No Drawings

METHOD FOR AMELIORATING MUSCLE WEAKNESS/WASTING IN A PATIENT INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS-TYPE 1

This application a 371 of PCT US 93/10063 Oct. 20, 1993.

TECHNICAL FIELD

The invention relates to the use of oxandrolone to attenuate myopathy and muscle weakness/wasting associated with infection by human immune deficiency virus-Type 1.

BACKGROUND OF THE INVENTION

Human immunodeficiency virus (HIV) associated myopathy and/or muscle weakness/wasting is a relatively common clinical manifestation of acquired immunodeficiency syndrome (AIDS). This is one of a number of neuromuscular disorders associated with the disease. There is some evidence to indicate that direct HIV infection of muscle may be at least partly responsible, occasionally resulting in a polymyositis-like disorder. In addition, zidovudine (AZT), an antiviral agent that is used widely in the clinical management of AIDS, has been associated with a toxic myopathy, presumably related to an inhibition of mitochondrial metabolism. In any event, the loss of muscle mass commonly observed in AIDS victims negatively impacts muscle function, however caused.

Individuals with HIV-associated myopathy or muscle weakness or wasting typically experience significant weight loss, generalized or proximal muscle weakness, tenderness, and muscle atrophy. Laboratory tests of samples from such individuals often reveal elevated levels of enzymes associated with muscle degeneration and necrosis, such as creatine kinase, aldolase, and aspartate amino transferase. Electromyographic test results for individuals with HIV-associated myopathy are typically consistent with myopathic changes. Histopathologic tests may reveal muscle fiber necrosis associated with lymphocytic inflammatory infiltrates. In AZT myotoxicity, ragged red fibers are often observed.

Clinical management of HIV-associated myopathy and muscle weakness/muscle wasting varies. In individuals with AZT myopathy, withdrawal of this anti-retroviral agent may be associated with temporary improvement in strength and muscle bulk. Corticosteroid therapy, such as the administration of prednisone, has been occasionally successful when inflammatory infiltrates have been detected in muscle. However, a potential drawback to this approach is that corticosteroids, because of their immunosuppressant activity, may be harmful to individuals with AIDS who are already dangerously immunosuppressed as a consequence of the HIV infection.

Furthermore, corticosteroid use itself is associated with myopathies and an increased susceptibility to infections. Plasmapheresis has also been used with some success, although at least one patient has experienced, despite an increase in muscle strength, substantial weakness over a period of several weeks.

SUMMARY OF THE INVENTION

The present invention provides a method which employs oxandrolone (an anabolic steroid with weak androgenic activity) as an alternative approach to the clinical management of HIV-associated myopathy/muscle weakness/muscle wasting. Loss in muscle mass (wasting) is attenuated, and body weight can be more readily maintained in this manner. Such an approach has been applied successfully to improve strength, reverse weight loss, and provide an improved sense of well-being.

Importantly, no evidence of liver injury or other untoward side effects have been observed.

Oxandrolone preferably is administered orally; however, other routes of administration can be utilized as well.

The present method of ameliorating muscle weakness or muscle wasting in a patient infected with HIV comprises administering to the patient daily a sufficient amount of oxandrolone to attenuate the patient's rate of muscle mass loss. To this end, oxandrolone may be administered, orally or otherwise, in a daily dose in the range of about 2.5 to about 20 milligrams. However, the response of individual patients may vary and in some instances a daily dose greater than 20 mg may be required to achieve the desired response. The daily dose may be divided into unit doses of about 1 to about 5 milligrams each, administered to the patient three times per day at about eight-hour intervals.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Oxandrolone (17-hydroxy-17-methyl-2-oxaandrostan-3-one) is a known compound that is commercially available. The preparation of oxandrolone is described, inter alia, in U.S. Pat. No. 3,128,283 to Pappo, which description is incorporated herein by reference.

Pharmacologically, oxandrolone is a synthetic anabolic steroid similar in structure to testosterone, but having a different, lesser androgenic/anabolic activity ratio. In addition, oxandrolone is unique among all other testosterone analogues in that it contains an oxygen atom instead of a methylene group at the 2-position of the phenanthrene nucleus. In addition, oxandrolone lacks a 4-ene function in its A-ring. The anabolic potency of oxandrolone, estimated as approximately 3 to 13 times that of testosterone, is believed to result form this unique structure.

Oxandrolone disposition and metabolism in man has been studied following oral administration of a 10 milligram dose. The study indicated that oxandrolone was rapidly and completely absorbed, yielding a mean peak plasma concentration of 417 micrograms of Oxandrolone per milliliter at 66 minutes. The plasma concentration of oxandrolone declined in a biphasic manner with a distribution half-life of approximately 30 minutes and an elimination half-life of 9.4 hours. Protein binding of oxandrolone was observed to be extensive.

In distinct contrast to other anabolic androgenic steroids such as methyltestosterone, fluoxymesterone, and micronized testosterone, oxandrolone taken orally is excreted mainly unchanged and unconjugated in urine. Urinary excretion of approximately 35 percent of an oral oxandrolone dose has been observed within 72 hours after ingestion. After 96 hours, approximately 65 percent of the administered oxandrolone dose was excreted in urine. Fecal excretion accounts for less than about 3 percent over the same time period.

Oxandrolone compositions, upon administration in accordance with this invention, ameliorate myopathy and muscle weakness in patients suffering from infections by human immunodeficiency virus-Type 1. Anabolic steroids, as a class, are known to stimulate appetite. Improved nutrition is important to individuals with AIDS who have experienced loss of lean body mass. Further, as a consequence of direct

interaction with androgen and/or glucocorticoid receptors in muscle, anabolic steroids promote muscle anabolism through both anabolic pathways and anticatabolic pathways.

Anabolic steroids, such as oxandrolone, also increase protein synthesis. For example, oxandrolone increased muscle protein synthesis in a study of acute uremic rats. Similarly, administration of oxandrolone preceded clinical improvement in appetite, cell mass, human growth, and weight for height in boys with chronic renal failure. These observations are consistent with anabolic activity. Oxandrolone may also stimulate the secretion of growth hormone and insulin-like growth factors.

In addition to producing beneficial direct anabolic action, oxandrolone is also believed to act as a delayed immunostimulant. In contrast, other appetite stimulants, such as dronabinol, that are currently under evaluation as appetite stimulants for AIDS patients can act as immunosuppressants in animals.

For purposes of administration in accordance with this invention, the active ingredient oxandrolone is combined with solid or liquid pharmaceutical carriers and formulated in unit dosage form using pharmacologically acceptable excipients, or dissolved or suspended in physiologically acceptable solvents or liquid vehicles for oral, percutaneous, or topical administration.

The overall daily dose of oxandrolone to provide a therapeutically effective amount in accordance with the method of this invention can be as low as about 2.5 milligrams and as high as about 20 milligrams, depending upon the patient's response and the mode of administration.

The amount of the active ingredient within the aforementioned ranges that is to be administered depends upon the age, weight and condition of the patient, as well as on factors such as the frequency and route of administration. In formulating oxandrolone, it is recognized that there may be differences between the immediate and the long term response. To account for these changes, the specific dosage given to a particular patient is based also on the individual patient's response. Preferably, oxandrolone is orally administered to the patient daily for a time period in the range of about 2 weeks to about 6 months.

Attenuation of the rate of muscle mass loss in a patient can be ascertained by comparing the patient's rate of weight loss before oxandrolone therapy with that after the administration of oxandrolone has been commenced. Alternatively, or in addition, the patient's urinary nitrogen level can be monitored, a well-known expedient. A decrease in the patient's urinary nitrogen level is indicative of a decrease in muscle mass loss.

Similarly, the maintenance of a relatively stable patient's total body potassium level, as well as an increase in the patient's total body potassium level, upon oxandrolone administration indicates that a therapeutically effective amount of oxandrolone is being administered. A patient's total body potassium level can be monitored, for example, as described in Kotler et al., The American Journal of Clinical Nutrition, 42:1255–1265 (December 1985) and Pierson, Jr., et al., Am. J. Physiol., 246 (Renal Fluid Electrolyte Physiol. 15) :F234–F239 (1984).

The route of administration can be oral, percutaneous, transdermal, sublingual, buccal, intravenous, intramuscular, or the like. Of these, oral administration is preferred. The patient's daily dose of the active ingredient preferably is in the range of about 7.5 milligrams, but may exceed 20 milligrams based on clinical response. This daily dose can be given in tablet form as a single dose, or as plural divided doses, preferably 2 to 3 divided doses. The requisite daily dose can also be supplied continuously, for example, by a transdermal patch worn by the patient or intravenously. If the oxandrolone is administered orally, dosages in the range of about 2 to about 5 milligrams three to four times daily typically may be prescribed.

Oxandrolone tablets are manufactured using standard solid dose form technology in accordance with United States Pharmacopeia (USP) specifications (see, for example, The United States Pharmacopeia, 22nd Revision, pp. 981–982). Specifically, a typical 150-milligram tablet contains the following:

Oxandrolone, USP	2.5 mg
Corn Starch, NF	30.0 mg
Lactose NF (hydrous)	113.0 mg
Hydroxypropyl Methylcellulose, USP	3.0 mg
Magnesium Stearate	1.5 mg
	150.0 mg

The terms "unit dosage form" and "unit dose" as used in the present specification and claims refer to a physically discrete unit or units suitable as unitary doses for patients, each unit containing a predetermined quantity of the active ingredient calculated to produce the desired therapeutic effect in association with the pharmacologically acceptable carrier. The specifications for the unit dosage forms of this invention are dictated in part and are also dependent upon (a) the unique characteristics of the active ingredient and (b) the particular therapeutic effect to be achieved, as well as upon limitations inherent in the art of compounding such active ingredient for the therapeutic use disclosed in detail in this specification. Examples of suitable unit dosage forms in accordance with this invention are tablets, pills, powder packets, wafers, cachets, segregated multiples of any of the foregoing, transdermal patches, aliquots of injectables, and the like forms.

The primary response variables are patient's total body potassium, body weight, muscle mass, muscle strength, improvement in or increased appetite, and general sense of well-being. In addition, improvement in immune status (or at a minimum, no worsening of immune function) in response to oxandrolone is significant as well.

An important question regarding the use of any drug in combination with anti-retroviral therapy is whether drug interactions may occur that would diminish AZT efficacy or increase the frequency of severity of AZT-related adverse reactions. TABLE 1 compares various published pharmacological parameters for oxandrolone and AZT and illustrates important differences between the two drugs.

TABLE 1

Comparison of Selected Oxandrolone and AZT Pharmacology Parameters

Parameter	Oxandrolone	AZT
Oral Bioavailability	100%	65%
Tmax	1.1 hr	0.7 hr
Biological T1/2	9.4 hr	1.1 hr
Vd	578 ml/kg	>1400 ml/kg
Protein Binding	>95%	25–35%
Plasma Clearance	43 ml/kg/hr	>1300 ml/kg/hr
Metabolism	Little	Extensive

TABLE 1-continued

Comparison of Selected Oxandrolone and AZT Pharmacology Parameters

Parameter	Oxandrolone	AZT
Glucuronidation	Little	Substantial
Urinary Excretion	Extensive; primarily parent compound	Extensive; parent and glucuronide conjugated
Target Organ Toxicity	Liver (anabolic steroids as a class)	Hematopoietic system (e.g., anemia, granulocytopenia)
Known Drug Interactions	Anticoagulants; oral hypoglycemic agents; adrenal steroid when edema present	Drugs that may: (a) inhibit glucuronidation (e.g., aspirin, acetaminophen) or urinary excretion (e.g., probenecid); (b) adversely affect blood cell number and function; and (c) nephrotoxic or cytotoxic

Because oxandrolone is primarily protein bound, whereas AZT is primarily non-protein bound, oxandrolone will not compete appreciably with AZT for binding sites in plasma. Consequently, administration of oxandrolone to patients on AZT therapy is unlikely to alter the level of free AZT in the blood. Likewise, the administration of AZT is unlikely to alter the level of free oxandrolone in the blood. An oxandrolone-AZT drug interaction involving binding site displacement is, therefore, extremely unlikely.

AZT is rapidly metabolized and excreted in the urine—a significant quantity is excreted in the form of glucuronide conjugates. In sharp contrast, oxandrolone, perhaps due to presence of a lactone group and the absence of a 4-ene function in the A-ring, undergoes little hepatic metabolism and is excreted primarily unchanged and unconjugated in urine. Thus, in contradistinction to other drugs that may competitively inhibit glucuronidation and thereby potentially slow the rate of AZT metabolism, such as aspirin, acetaminophen, or indomethacin, the present active agent, oxandrolone, is not believed to affect AZT metabolism.

Furthermore, oxandrolone is neither nephrotoxic nor cytotoxic. Accordingly, oxandrolone is not expected to interfere with the renal excretion of AZT or its metabolites. To the contrary, oxandrolone has been safely and effectively used in patients with chronic renal disease to stimulate growth and increase lean body mass. In well-controlled studies of oxandrolone for the clinical management of critically ill patients with acute alcoholic hepatitis, oxandrolone administered at daily doses of up to 80 mg/day for four weeks and 40 mg/day for eight weeks did not result in any drug-related nephrotoxicity.

While it is known that anabolic androgenic steroids have been associated with potentially life-threatening forms of liver disease, including peliosis hepatis, cholestatic jaundice, and hepatocellular neoplasms, specific reports in the medical literature regarding liver disease in oxandrolone-treated patients, at the dosages proposed for use in the clinical management of HIV associated muscle weakness/wasting (i.e., about 2.5 to about 20 mg/day) are rare.

Oxandrolone and AZT have different mechanisms of action. They also function in different sites of cellular action at the receptor level. Oxandrolone functions via interaction with androgen and glucocorticoid receptors, whereas AZT, once phosphorylated, acts to inhibit HIV reverse transcription. Thus, competitive inhibition of AZT by oxandrolone at the cellular level also is considered unlikely.

Neither has oxandrolone been associated with anemia or granulocytopenia, two frequently occurring and potentially serious side effects associated with AZT therapy. To the contrary, anabolic androgenic steroids have been used clinically to stimulate ethyropoiesis in hypoanemias, aplastic anemias, hemolytic anemias, renal anemias, anemias due to cytotoxic therapy, and various leukemias. It has been reported recently that androgens augment beneficial effects of erythropoietin in the treatment of anemia resulting from end-stage renal disease.

Data derived from animal models and human clinical studies indicate that anabolic steroids are unlikely to suppress immune function in patients infected with HIV. For example, anabolic steroids can stimulate granulopoiesis in mice, as evidenced by stimulation of granulocytic colony-forming cells derived from spleen and bone marrow. Similarly, an anabolic steroid known as nandrolone decanonate enhanced macrophage activity and cell-mediated immunity in patients with uterine cervical cancer when administered parentally. In related studies, anabolic steroids increased peripheral lymphocyte and monocyte counts, Immunoglobin G (IgG) levels, and PHA-blastoid transfromation of peripheral lymphocytes. In those studies, β_2-microglobulin levels simultaneously decreased.

IgG is one of a class of antibodies secreted by B cells (i.e., B-lymphocytes) in response to an antigenic challenge (e.g., foreign protein like that from bacteria). In the case of HIV infection, humoral immune function (i.e., B-cell mediated) is significantly impaired. Accordingly, when HIV-infected individuals are challenged with a specific antigen, the typical response of B-cell proliferation, differentiation and secretion of antibodies (e.g., IgG) is diminished or absent. This decline in humoral immune function coupled with defects in cellular immune (i.e., T-cell) function contributes to the overall failure of the immune system to respond in an appropriate manner to challenge. B-cells in AIDS victims are, by mechanisms unknown, hyperstimulated to secrete large amounts of immunoglobulins that make the humoral system refractory to new antigens. The result is that the patient's system no longer recognizes new antigens and does not respond.

In animal studies in which anabolic steroids have been reported to increase IgG and PHA-blastoid activity, these changes occurred as a result of immune system stimulation, and are positive responses. β-microglobin is a cell surface protein that is found on all nucleated calls and it is released into the serum during cell turnover. Generally, β-microglobulin is considered a marker of infectious, inflammatory, malignant and autoimmune disease activity. In several AIDS studies, β-microglobulin levels correlated with disease progression and T4 (T-helper) cell counts. In the case of therapy with oxandrolone, for example, a decrease in β-microglobulin levels is desirable. Thus, animal data showing reduced plasma levels of β-microglobulin in response to anabolic steroids is evidence of a positive effect and suggestive of similar activity in man.

Accordingly, there are no reasons to believe that the administration of an anabolic steroid in general and oxandrolone in particular would have adverse effects on the immune system. Generally, the target organ of toxicity for these drugs is the liver—probably because this is where most are metabolized. Oxandrolone, however, has a remarkably good safety profile in man as a likely consequence of its resistance to hepatic metabolism; an oral dose is excreted primarily in urine as the parent compound, as stated hereinabove.

Data from clinical trials in patients with severe alcoholic liver disease provide further evidence that oxandrolone is

not likely to suppress immune function in patients with HIV infection. Ethanol abuse is associated with loss of lymphocyte functions, particularly T-cell dependent immune responses. Previous researchers have observed that oxandrolone significantly improved lymphocyte number in patients with severe alcoholic hepatitis. Because the loss of lymphocytic function by alcoholic liver disease parallels, to a significant degree, the loss of T-cell function due to HIV infection, it is reasonable to hypothesize that oxandrolone will increase the T-Cell function of HIV-infected patients.

Therefore, these data from laboratory animals and human studies indicate that suppression of the immune system by anabolic steroids, such as oxandrolone, is unlikely. Nonetheless, subjects undergoing oxandrolone therapy, as a precaution, should be monitored for changes in lymphocyte number, particularly CD4+ and CD8+, as is routinely done for patients who undergo steroid therapy.

In summary, based on the differences between AZT and oxandrolone with respect to pharmacokinetics, metabolism, reported drug interactions, mechanisms of action, and reported toxicities, oxandrolone and AZT can be safely used in combination for subjects infected with the Type-1 HIV virus and suffering from HIV-associated myopathy. The use of oxandrolone in patients on AZT therapy is, on the basis of known drug interactions, also consistent with current FDA-approved labeling for AZT and oxandrolone.

The following example demonstrates the effectiveness of oxandrolone in attenuating the effects of HIV-associated muscle weakness or muscle wasting in an AIDS patient.

EXAMPLE

A patient, a thirty-two year old homosexual man, known to be HIV-seropositive since February 1989, noted difficulty opening drawers and bottles in May 1989. The patient weakened progressively and, during a physical examination in September 1989, demonstrated by confrontation testing the weakness of neck flexion and proximal limbs. However, his muscle stretch reflexes remained normal. Laboratory tests showed the patient's creatine kinase level to be 286 International Units per liter, much higher than the normally observed range for creatine kinase of about 40–200 Units per liter.

Zidovudine (azidothymidine or AZT) was initiated at 500 milligrams daily, but the patient's strength continued to decline through February 1990. He complained of an inability to ascend a flight of stairs. The patient exhibited greater weakness and atrophy of neck flexors and extremity muscles during another physical examination performed at this time. An electromyogram revealed a decrease of amplitude and duration of the patient's motor unit potentials and increased recruitment in selected muscles of his right upper extremity. The patient's creatine kinase tested at 456 Units per liter. A muscle biopsy revealed numerous myofibers, abundant ragged red fibers, and numerous eosinophilic inclusions. Round cell inflammatory infiltrates were also noted. In light of these developments, the zidovudine treatment was terminated.

Substantial improvement initially followed the discontinuation of zidovudine. However, because of a subsequent continued and progressive weakness rendering it difficult for the patient to ascend or descend a flight of stairs, a prednisone therapy (60 mg daily) was initiated. No significant improvement accompanied the use of prednisone.

Thereafter, a trial period of oral oxandrolone administration (2.5 milligrams, three times daily, in tablet form) was initiated. Within two weeks of the initiation of the oxandrolone therapy, the patient noted an improved sense of well being, became stronger, and gained weight. Within one month, he was able to ascend and descend stairs without problems. Confrontation testing revealed nearly normal strength. The patient's weight increased from 115 pounds to 130 pounds. The patient's muscle atrophy was alleviated as well. Liver functions were closely monitored for signs of elevation, but undesirable side effects were not detected.

After several months of the aforementioned therapy with oxandrolone, the patient was no longer able to obtain oxandrolone for use as a medication. Weakness and weight loss ensued. Trials of other anabolic preparations, specifically stanazol and oxymethalone, did not return the patient to his previous levels of function and strength.

The EXAMPLE demonstrates that oxandrolone can be a beneficial alternative for clinical management of HIV-associated myopathy and muscle weakness and wasting.

It is intended that the foregoing description is by way of illustration only and is not to be construed as limiting the invention in any way except in the spirit and scope of the appended claims.

What is claimed is:

1. A method for ameliorating HIV-associated myopathy and muscle weakness in an AIDS patient which comprises orally administering oxandrolone to the AIDS patient in a daily dosage of between about 2.5 to about 7.5 milligrams.

2. The method in accordance with claim 1 wherein the daily dosage of the oxandrolone is about 7.5 milligrams.

3. The method in accordance with claim 1 wherein the oxandrolone is administered to said patient as a unit dose of about 1 to about 2.5 milligrams three times per day at about eight-hour intervals.

4. The method in accordance with claim 1 wherein the oxandrolone is administered in the form of a tablet.

5. The method in accordance with claim 1 wherein administration is continued over a period of about 2 weeks.

6. The method in accordance with claim 1 wherein administration is continued over a period of about 2 weeks.

7. The method in accordance with claim 3 wherein administration is continued over a period of about 2 weeks.

8. A method for ameliorating HIV-associated myopathy and muscle wasting in an AIDS patient which comprises orally administering a therapeutically effective amount of oxandrolone to the AIDS patient daily for a time period of about 2 weeks.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,090,799
DATED : Jul. 18, 2000
INVENTOR(S) : Joseph R. Berger

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On title page, item [73] should read --Bio-Technology General Corp.--

Signed and Sealed this

Thirty-first Day of October, 2000

Attest:

Q. TODD DICKINSON

Attesting Officer

Director of Patents and Trademarks

EXHIBIT C

US006576659B1

(12) **United States Patent**
Fishbein

(10) **Patent No.: US 6,576,659 B1**
(45) **Date of Patent: *Jun. 10, 2003**

(54) **USE OF OXANDROLONE IN THE TREATMENT OF BURNS AN OTHER WOUNDS**

(75) Inventor: **Don Fishbein**, Westfield, NJ (US)

(73) Assignee: **Bio-Technology General Corp.**, Middlesex, NJ (US)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/985,734**

(22) Filed: **Dec. 5, 1997**

Related U.S. Application Data

(60) Provisional application No. 60/032,414, filed on Dec. 5, 1996.

(51) **Int. Cl.**[7] **A61K 31/35**
(52) **U.S. Cl.** **514/453**
(58) **Field of Search** 514/175, 453

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Marmo et al., Gazzetta Medica Italiana (in Italian) (1974) 133: 47–56 —Exhibit 13a English Translation (Exhibit 13/13A).
Albanese et al., Nutritition Report International (1970) 1(4): 231–242 (Exhibit 14).
O'Shea et al., Nutrition Report International (1970) 2(6): 351–362 (Exhibit 15).

* cited by examiner

Primary Examiner—Jerome D. Goldberg
(74) *Attorney, Agent, or Firm*—John P. White; Cooper & Dunham LLP

(57) **ABSTRACT**

The subject invention provides a method of treating burn-induced weight loss in a burn patient which comprises administering a therapeutically effective amount of an oxandrolone to the patient. The invention also provides a method of treating a wound in a patient suffering from a wound which comprises administering a therapeutically effective amount of an oxandrolone to the patient. The subject invention further provides a method of treating burn-induced weight loss in a burn patient which comprises administering a therapeutically effective amount of an oxandrolone in conjunction with a protein supplement to the patient.

20 Claims, 9 Drawing Sheets

FIGURE 1

RESPONSE TO BURN INJURY, MET-Rx, OXANDRIN

	CATABOLIC PHASE					ANABOLIC PHASE						
	AGE	BURN % BSA	CATABOLIC PHASE (DAYS)	WEIGHT LOSS (LBS)	%TOTAL	ONSET	ENERGY LEVEL			THERAPY INDEX		
							1	2	3 (wks)	1	2	3 (wks)
GROUP 1 (n=10)	25±9	35±9	38±9	30±5	18±3	1	2±1	2±1	3±2	2±1	3±1	3±1*
GROUP 2 (MET-Rx n=7)	28±8	38±9	37±11	28±6	17±4	2	4±1*	6±2*	7±2*	3±1	6±1*	6±2*
GROUP 3 (MET-Rx, Oxandrin n=4)	27±10	37±10	36±10	29±5	18±4	3	5±1*	8±2*	8±2*	4±1*	7±1*	8±2*

*significant difference between groups $p<0.05$

RESPONSE TO BURN INJURY, MET-Rx, OXANDRIN

	CATABOLIC PHASE NUTRITIONAL PROFILE					ANABOLIC PHASE					
	Cal+ kg/day	Prot g/kg/day	Cal/kg/day*			Prot/g/kg/day			Weight Gain (lbs)		
			1	2	3 (wks)	1	2	3 (wks)	1	2	3(wks)
GROUP 1 (n=10)	30±2	1.9±0.02	22±2	23±2	23±3	1.3±0.1	1.3±0.1	1.2±0.1	1.2±0.1	1.3±0.2	1.4±0.2
GROUP 2 (n=7)	31±3	2.0±0.2	24±3	27±2*	28±3*	2.0±0.2	2.1±0.1	2.2±0.2	2.5±0.2*	2.7±0.1*	2.9±0.2*
GROUP 3 (n=4)	31±3	1.9±0.1	25±2	28±2*	30±3*	2.1±0.1	2.1±0.1	2.2±0.1	4.9±0.5*	5.0±0.5*	5.1±0.5*

*significant difference between groups $p<0.05$
*non-protein calories

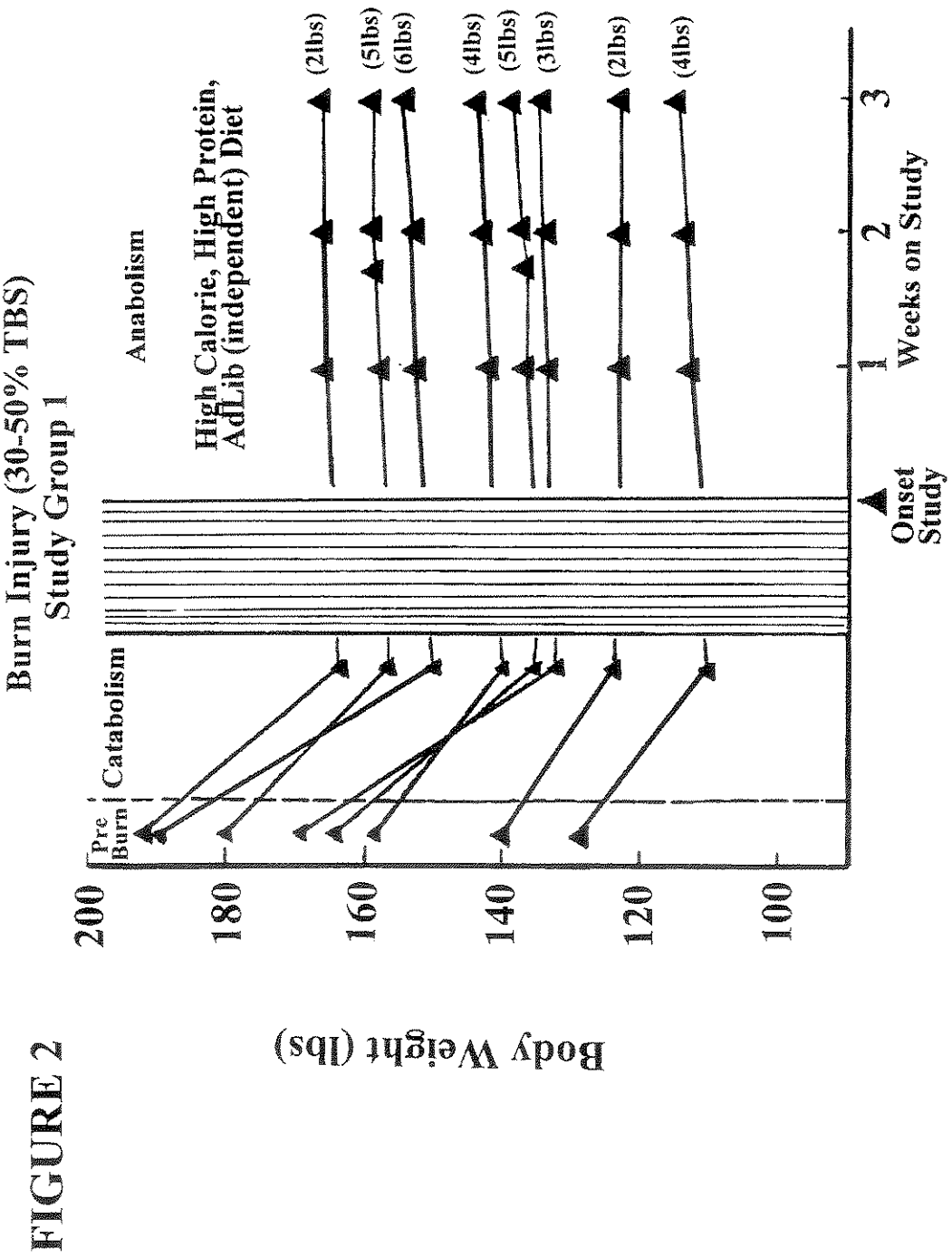

Burn Injury (30-50% TBS)
Study Group 1
Anabolism
Catabolism
Pre Burn
High Calorie, High Protein, AdLib (independent) Diet
(2lbs)
(5lbs)
(6lbs)
(4lbs)
(5lbs)
(3lbs)
(2lbs)
(4lbs)
Onset Study
1
2
3
Weeks on Study
200
180
160
140
120
100
Body Weight (lbs)

FIGURE 2

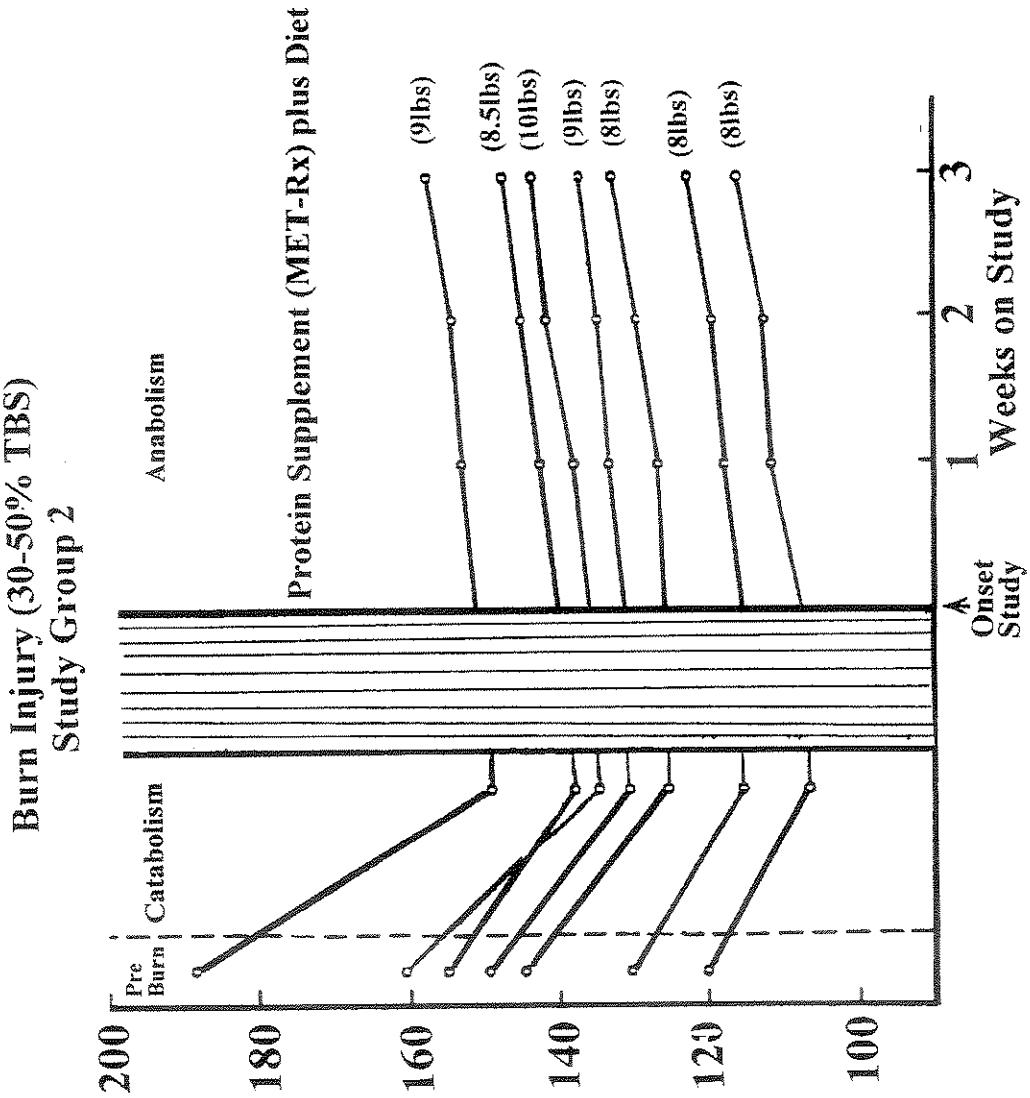

Burn Injury (30-50% TBS)
Study Group 2
Anabolism
Protein Supplement (MET-Rx) plus Diet
(9lbs)
(8.5lbs)
(10lbs)
(9lbs)
(8lbs)
(8lbs)
(8lbs)
Catabolism
Pre Burn
Onset Study
1
2
3
Weeks on Study
200
180
160
140
120
100
Body Weight (lbs)

FIGURE 3

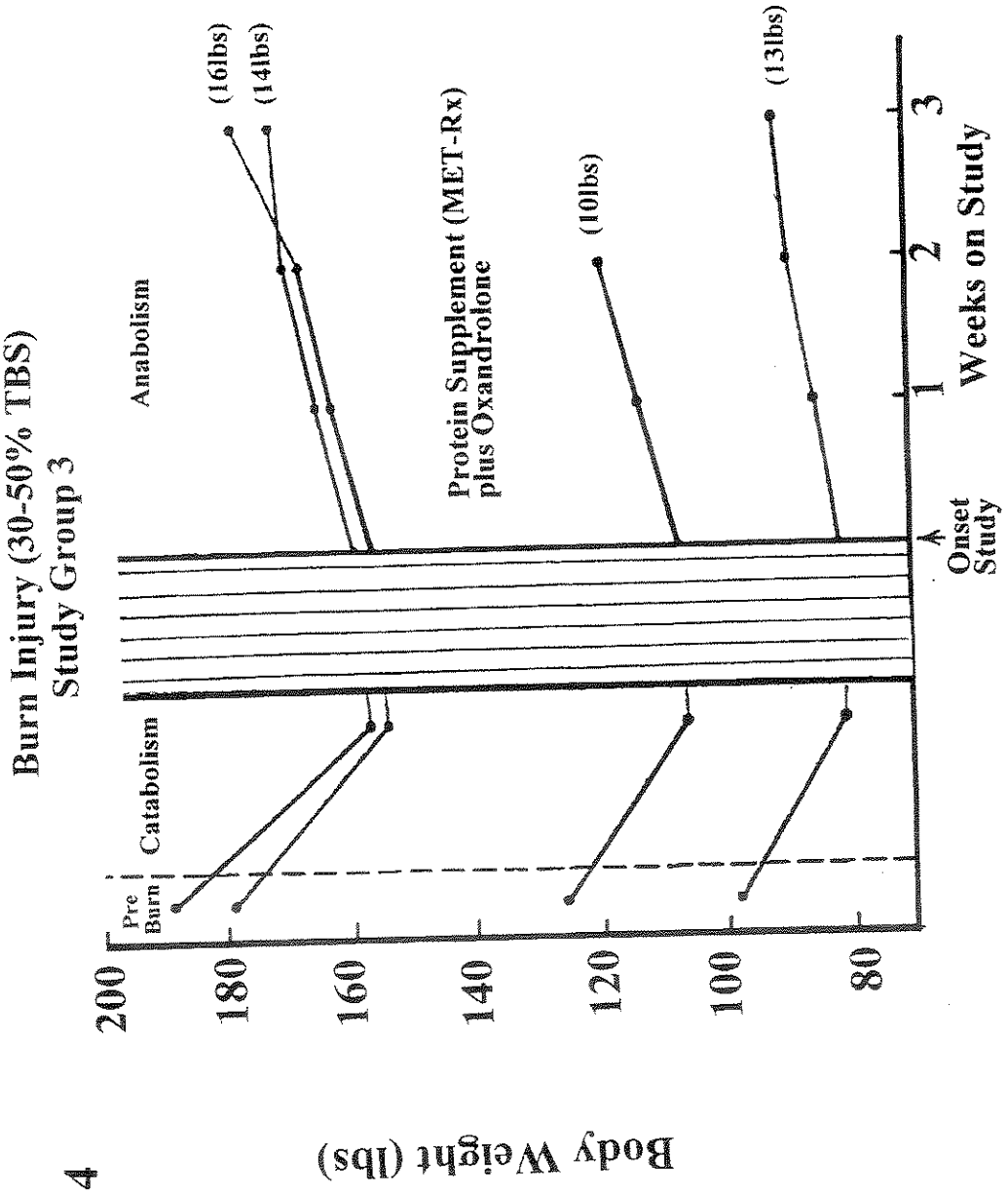

Burn Injury (30-50% TBS)
Study Group 3
Anabolism
Catabolism
Pre Burn
(16lbs)
(14lbs)
Protein Supplement (MET-Rx)
plus Oxandrolone
(10lbs)
(13lbs)
Onset Study
Weeks on Study
1
2
3
200
180
160
140
120
100
80
Body Weight (lbs)

FIGURE 4

FIGURE 5

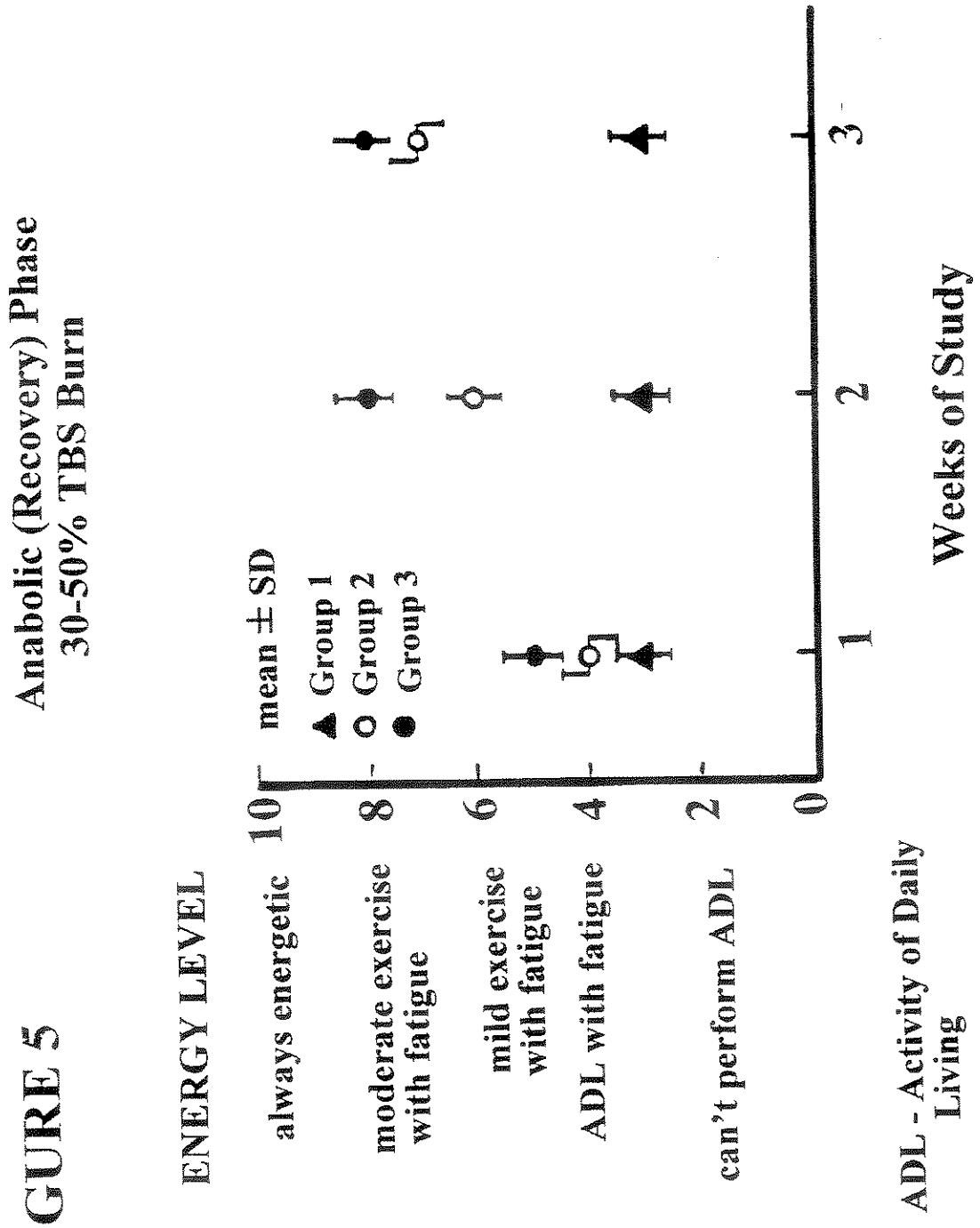

Anabolic (Recovery) Phase
30-50% TBS Burn
ENERGY LEVEL
always energetic
moderate exercise with fatigue
mild exercise with fatigue
ADL with fatigue
can't perform ADL
ADL - Activity of Daily Living
mean ± SD
Group 1
Group 2
Group 3
10
8
6
4
2
0
1
2
3
Weeks of Study

FIGURE 6

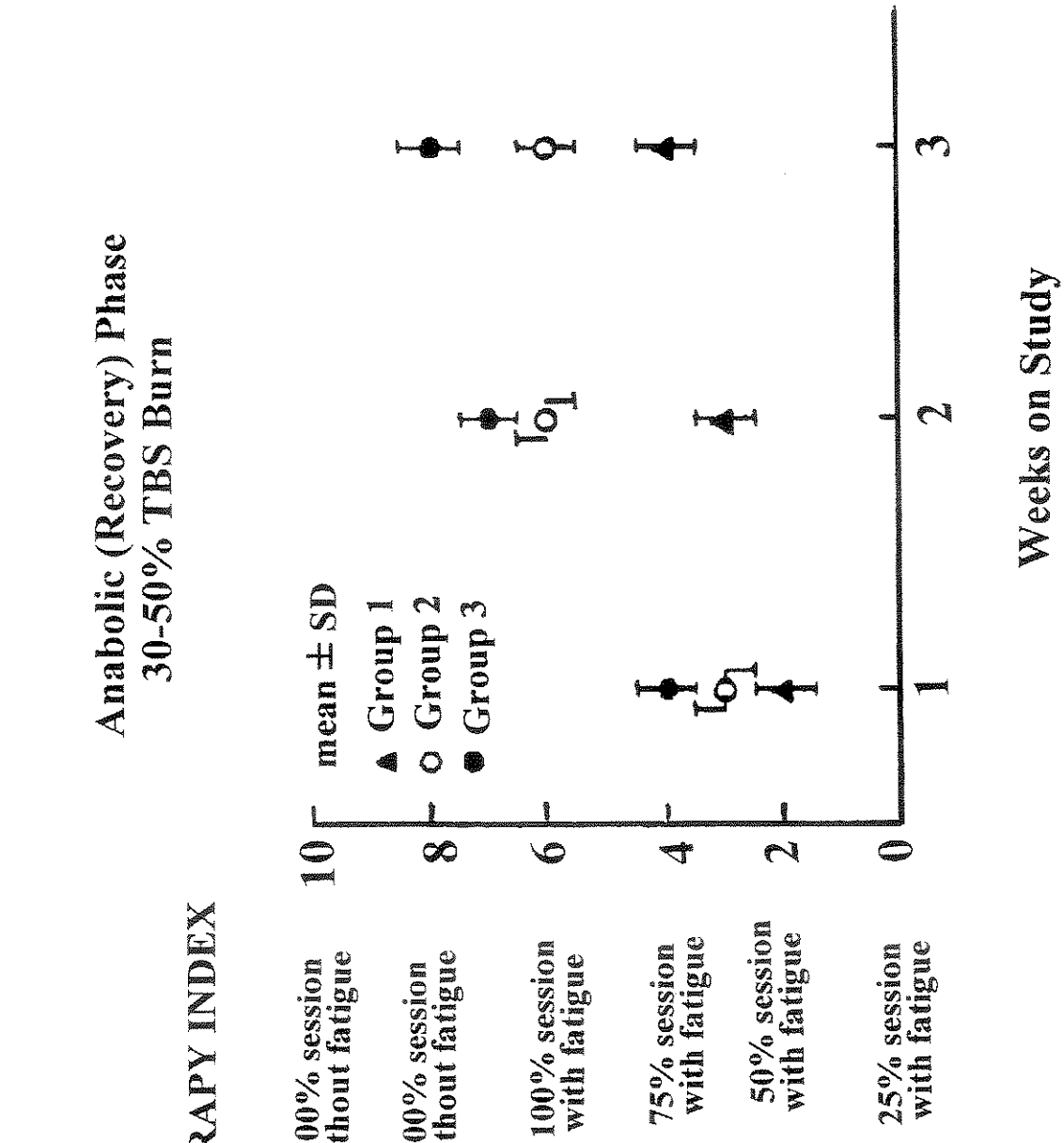

Anabolic (Recovery) Phase
30-50% TBS Burn
THERAPY INDEX
mean ± SD
Group 1
Group 2
Group 3
>100% session without fatigue
100% session without fatigue
100% session with fatigue
75% session with fatigue
50% session with fatigue
25% session with fatigue
10
8
6
4
2
0
1
2
3
Weeks on Study

FIGURE 7

EFFECT OF ANABOLIC AGENT AND INCREASED PROTEIN CONTENT ON THE RECOVERY PHASE

	CATABOLIC PHASE					RECOVERY (ANABOLIC) PHASE (WKS)								
						NUTRITIONAL PROFILE						WEIGHT GAIN		
						Cal/kg/day[+]			Prot/g//kg/day			Pounds Per Week		
	AGE	BURN %BSA	DAYS	WT. LOSS LBS.	%TOTAL	1	2	3	1	2	3	1	2	3
Group 1 (n=6)	34±8	45±8	39±9	20±7	12±4	32±4	34±4	35±5	1.9±0.1	2±0.2	2.2±0.1	2.5±0.2	2.6±0.4	2.6±0.5
Group 2 (n=7)	36±9	47±6	35±9	21±6	11±3	33±3	33±4	34±4	2.0±0.2	2.0±0.2	2.2±0.2	3.9±0.4*	4.4±0.5*	4.8±0.5*
Group 3 (n=10)	39±8	42±7	32±10	19±8	11±6	34±3	33±3	33±5	1.5±0.2[+]	1.4±0.2[+]	1.4±0.3[+]	1.2±0.1[+]	1.3±0.2[+]	1.4±0.2[+]

*significant difference between groups 1 and 2 $p<0.05$
[+]significant difference between groups 1 and 3 $p<0.05$

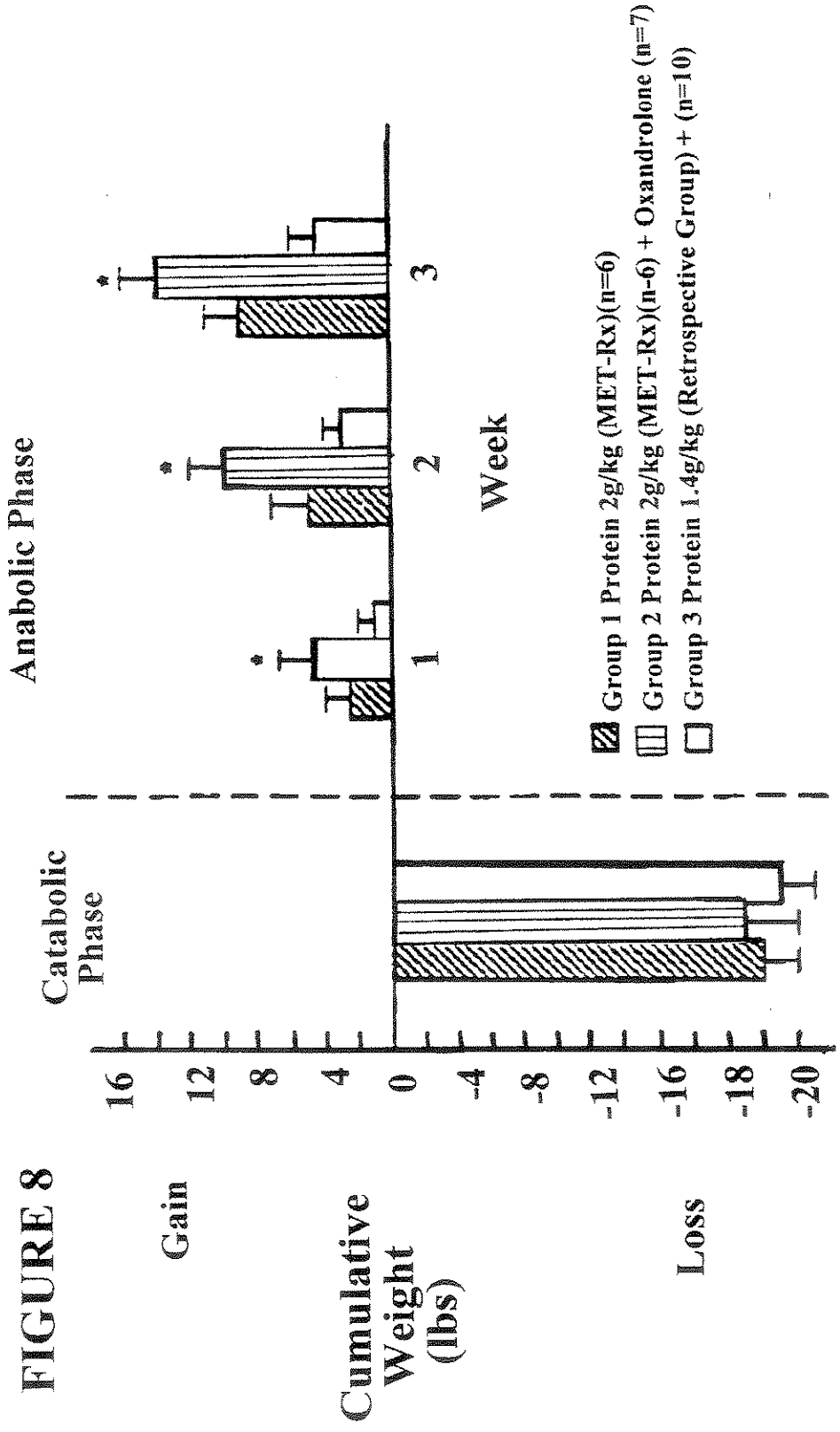
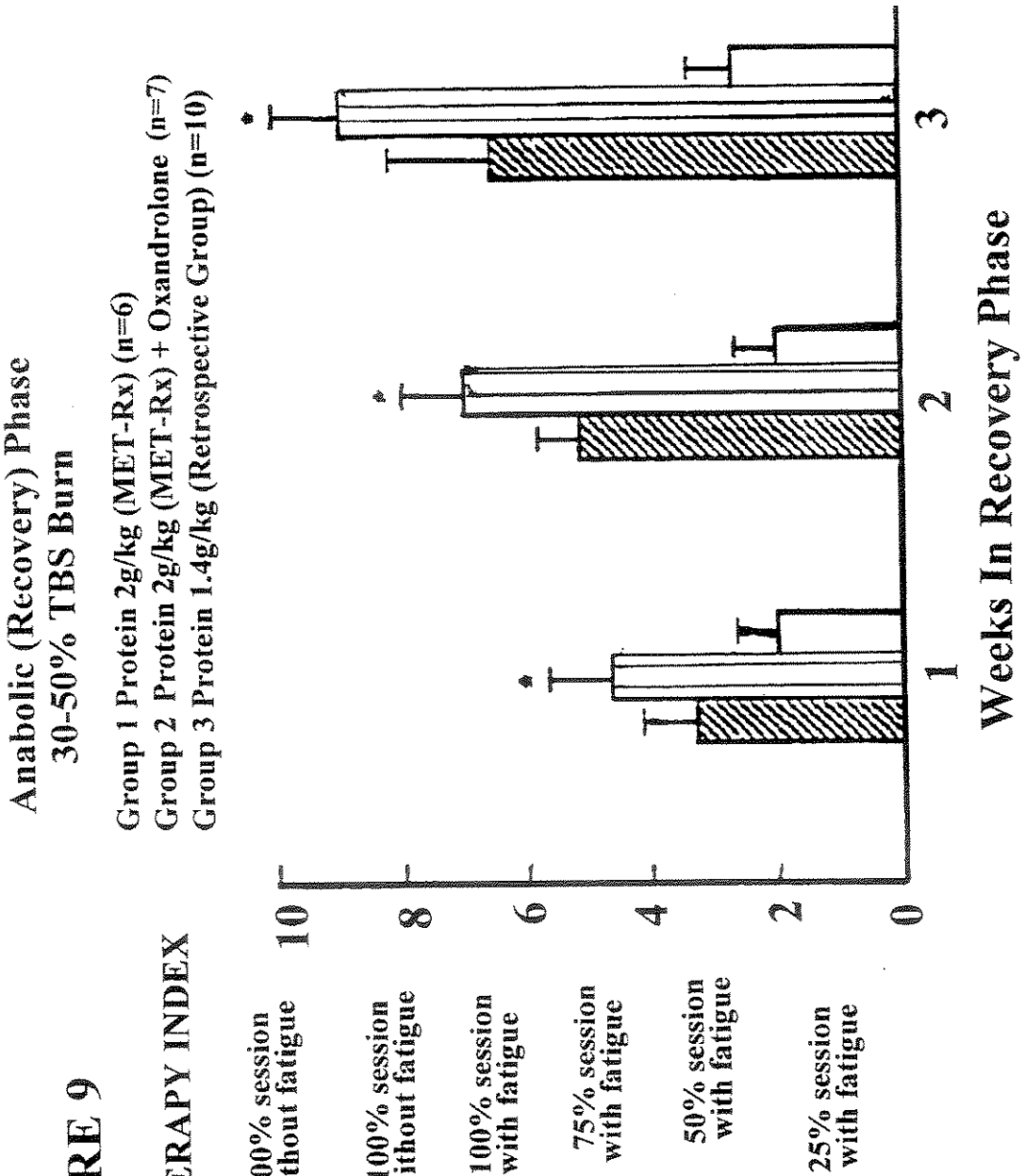

Anabolic Phase
Catabolic Phase
Week
1
2
3
*
*
*
16
12
8
4
0
-4
-8
-12
-16
-18
-20
Gain
Loss
Cumulative Weight (lbs)
Group 1 Protein 2g/kg (MET-Rx)(n=6)
Group 2 Protein 2g/kg (MET-Rx)(n-6) + Oxandrolone (n=7)
Group 3 Protein 1.4g/kg (Retrospective Group) + (n=10)

FIGURE 8

FIGURE 9


Anabolic (Recovery) Phase
30-50% TBS Burn
Group 1 Protein 2g/kg (MET-Rx) (n=6)
Group 2 Protein 2g/kg (MET-Rx) + Oxandrolone (n=7)
Group 3 Protein 1.4g/kg (Retrospective Group) (n=10)
THERAPY INDEX
>100% session without fatigue
100% session without fatigue
100% session with fatigue
75% session with fatigue
50% session with fatigue
25% session with fatigue
0
2
4
6
8
10
1
2
3
Weeks In Recovery Phase

USE OF OXANDROLONE IN THE TREATMENT OF BURNS AN OTHER WOUNDS

This application claims priority of U.S. Provisional Application Ser. No. 60/032,414, filed Dec. 5, 1996, the contents of which are hereby incorporated into this application by reference.

Throughout this specification, various publications are referenced by Arabic numerals within parentheses. Full citations for these references may be found at the end of the specification immediately preceding the claims. The disclosure of these publications in their entireties are hereby incorporated by reference into this specification in order to more fully describe the state of the art to which this invention pertains.

BACKGROUND OF THE INVENTION

Burns

Over one million people are involved in burn accidents in the United States each year. Approximately 150,000 of these patients are hospitalized and over 6000 of these die each year (1).

Following thermal injury, severe protein and fat wasting occurs (1). Loss of as much as 20% of body protein may occur in the first two weeks following major burn injury (2). Increased oxygen consumption, metabolic rate, urinary nitrogen excretion, fat breakdown and steady erosion of body mass are all directly related to burn size and return to normal as the burn wound heals or is covered (1). The metabolic rate in patients with burns covering more than 40% of total body surface is twice as high as the metabolic rate in people without burns (1).

Although the danger associated with acute burn-induced weight loss, especially lean body mass has well been defined, the impact of this process on patient outcome continues to be severely underestimated. The focus of management of critical illness post-burn remains that of cardiopulmonary support and infection control while stress induced catabolism may proceed unchecked leading to a rapid loss of lean tissue (fat-free), mainly muscle which is followed by protein loss in diaphragm, heart, then liver, kidney and splanchnic bed. The loss of visceral proteins may actually begin very early after injury and the muscle protein is used to replace organ losses. It is clear that the response to severe injury or post-surgical infection will become autodestructive if not contained. Complications will occur including multiple organ dysfunction, the leading cause of death in the post-burn period. A loss of lean body mass exceeding 40% of total is usually fatal. This muscle loss corresponds to a comparable loss of total body protein which affects all organ functions.

Although major advances in surgical nutrition have also been made, attempt at controlling the protein loss often come too little and too late to prevent the catabolism induced complications. The degree of lean tissue loss corresponds very precisely with not only profound weakness, including chest wall and diaphragm impairment, but also decreased immune function, leading to infection, usually pneumonia.

Both lymphocyte and neutrophil immune defenses are impaired. Loss of myocardial muscle leads to decreased contractility. Wound healing becomes markedly impaired and an open wound soon becomes an infected wound. Cell metabolic abnormalities occur including decreased cell energy charge and impaired calcium kinetics.

Despite this well defined concept, a routine assessment of body weight and body protein loss and an aggressive attempt at preventing early protein depletion by controlling the host response to injury and optimizing anabolism is not performed.

The current therapy of burn injury, namely high protein nutrition and early wound closure attenuates the process but patients with large burns enter the recovery phase with a significant deficit in muscle mass. Since the peak rate of restoration of muscle mass, using endogenous stimuli alone, including good nutrition approximates 1 to 1.5 pounds a week, restoration of lean body mass usually requires months.

Use of the anabolic agent, human growth hormone, can increase anabolic activity in the burns, but high expense and complications such as hyperglycemia have prevented widespread use of this agent (3). This agent also has to be administered by injection.

Since the rate of recovery of lean body mass dictates disability time, an increased rate would be of tremendous functional and economic value in burn patients.

The subject invention provides therapies that increase the rate of recovery of lean body mass, thereby reducing the length of stay in a hospital and reducing rehabilitation time. Moreover, the subject invention provides therapies that increase the rate of wound healing. This is of great importance in burn-patients, especially in those patients that receive skin grafts. This is also important in burn-patients which have wounds at donor sites.

Oxandrolone

Oxandrolone(17-methyl-17-hydroxy-2-oxa-5-androstan-3-one) is a known compound which is commercially available. The preparation of oxandrolone is described, inter alia, in U.S. Pat. No. 3,128,283. Oxandrolone is an anabolic steroid synthetically derived from testosterone. Oxandrolone has a unique chemical structure compared with other testosterone analogs. Oxandrolone contains an oxygen rather than a carbon atom at the 2-position within the phenanthrene nucleus (4) and lacks a 4-ene function in the A-ring. The anabolic activity of oxandrolone is approximately 6 times greater than its androgenic activity and has been found to be 6.3 times greater than that of methyltestosterone (4).

Anabolic activity refers to the ability to cause nitrogen retention, promoting weight gain and increasing muscle strength. Androgenic activity refers to the ability to enhance male characteristics (i.e. secondary sex characteristics such as facial hairs and voice changes). Because of the high ratio of anabolic to androgenic activity, oxandrolone is less likely to cause adverse cosmetic consequences in women than many testosterone analogs.

Furthermore, in contrast to the majority of oral androgenic anabolic steroids (e.g. micronized testosterone, methyltestosterone, fluoxymesterone), oxandrolone undergoes relatively little hepatic metabolism (5, 6).

Oxandrolone has been administered to malnourished patients with alcoholic hepatitis (7, 8). Oxandrolone has been shown to be safe even in dosages of up to 80 mg/day in patients with alcoholic hepatitis (7).

The subject invention discloses the use of an oxandrolone for the treatment of cachexia, muscle wasting and involuntary weight loss associated with wounds, especially burns.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1: Effect of oxandrolone and increased protein content on the recovery phase in burn patients (Example 1): measurements of energy level, therapy index and weight gain of burn patients in Groups 1, 2 and 3.

FIG. 2: Body weight of patients (Example 1) with burn injury in Group 1.

FIG. 3: Body weight of patients (Example 1) with burn injury in Group 2.

FIG. 4: Body weight of patients (Example 1) with burn injury in Group 3.

FIG. 5: Energy level (0–10) of burn patients (Example 1) in Groups 1, 2 and 3.

FIG. 6: Therapy index (0–10) of burn patients (Example 1) in Groups 1, 2 and 3.

FIG. 7: Effect of oxandrolone and increased protein content on the recovery phase in burn patients (Example 2): measurements of weight gain in Groups 1, 2 and 3.

FIG. 8: Body weight of patients (Example 2) with burn injury in Groups 1, 2 and 3.

FIG. 9: Therapy index (0–10) of burn patients (Example 2) in Groups 1, 2 and 3.

SUMMARY OF THE INVENTION

The invention also provides a method of treating a wound in a patient suffering from a wound which comprises administering a therapeutically effective amount of an oxandrolone to the patient.

The subject invention provides a method of treating burn-induced weight loss in a burn patient which comprises administering a therapeutically effective amount of an oxandrolone to the patient.

The subject invention further provides a method of treating burn-induced weight loss in a burn patient which comprises administering a therapeutically effective amount of an oxandrolone in conjunction with a protein supplement to the patient.

DETAILED DESCRIPTION OF THE INVENTION

Oxandrolone as used herein encompasses 17-methyl-17-hydroxy-2-oxa-5-androstan-3-one (both racemic mixtures and optically active enantiomers) as well as pharmaceutically acceptable esters thereof. For example, an oxandrolone product which is commercially available is the Oxandrin® tablet from BTG Pharmaceuticals Corp., Iselin, N.J. 08830, which is 17α-methyl-17β-hydroxy-2-oxa-5α-androstan-3-one. This product was used throughout the studies described herein.

Protein supplement as used herein encompasses any nutritionally effective protein supplement including commercially available protein supplements.

Protein supplement Met-Rx™ contains 74 gram/liter protein, 48 gram/liter carbohydrate and 8 gram/liter fat.

A wound as used herein is a breach in the continuity of skin tissue. Examples of wounds are punctures, incisions, excisions, lacerations, abrasions, ulcers and burns. Examples of ulcers as used herein are ulceration of the heel in a diabetic patient and decubitus ulcers in bedridden patients.

A skin graft as used herein encompasses an autograft or an allograft.

Oxandrolone may be administered orally, intravenously, intramuscularly, subcutaneously, topically, intratracheally, intrathecally, intraperitoneally, rectally, vaginally or intrapleurally.

If oxandrolone is administered orally, it is administered in the form of a tablet, a pill, a liquid or a capsule.

A liquid may be administered in the form of a solution or a suspension.

The compositions produced in accordance with the invention may comprise conventional pharmaceutically acceptable diluents or carriers. Tablets, pills, liquids and capsules may include conventional excipients such as lactose, starch, cellulose derivatives, hydroxypropyl methylcellulose and magnesium stearate. Suppositories may include excipients such as waxes and glycerol. Injectable solutions will comprise sterile pyrogen-free media such as saline and may include buffering agents, stabilizing agents, solubilizing agents or preservatives. Conventional enteric coatings may also be used.

Compositions for topical administration may be in the form of creams, ointments, lotions, solutions, transdermal delivery systems, transdermal patches or gels.

The subject invention provides a method of treating burn-induced weight loss in a burn patient which comprises administering a therapeutically effective amount of an oxandrolone to the patient.

The subject invention further provides a method of treating burn-induced weight loss in a burn patient which comprises administering a therapeutically effective amount of an oxandrolone in conjunction with a protein supplement to the patient.

The subject invention provides a use of an oxandrolone in the preparation of a composition to treat burn-induced weight loss in a burn patient. This composition may optionally comprise a protein supplement.

In a preferred embodiment, the amount of oxandrolone is about 1–100 mg per day.

In especially preferred embodiments, the amount of oxandrolone is about 20 mg per day or about 80 mg per day.

The oxandrolone may be administered in a solid dosage form, in a liquid dosage form, in a sustained-release formulation or in a once a day formulation. The liquid dosage form may inter alia be alcohol-based or formulated with a cyclodextrin such as hydroxypropyl-β-cyclodextrin.

The invention further provides a method of treating a wound in a patient suffering from a wound which comprises administering a therapeutically effective amount of an oxandrolone to the patient.

The subject invention provides a method of improving the rate of healing of a wound in a patient suffering from a wound which comprises administering a therapeutically effective amount of an oxandrolone to the patient.

The subject invention further provides a use of an oxandrolone in the preparation of a composition to treat a wound in a patient suffering from a wound.

The subject invention also provides a use of an oxandrolone in the preparation of a composition to improve the rate of healing of a wound.

The subject invention also describes the use of oxandrolone in the maintenance and restoration of lean body mass in burn and trauma patients.

The wound may be a burn wound, an ulcer especially a decubitus ulcer (pressure sore), a skin graft or any form of wound including a traumatic wound.

Oxandrolone may be administered in conjunction with glutamine or human growth hormone.

The subject invention further provides a composition for use in topical treatment of wounds comprising an oxandrolone and a pharmaceutically acceptable carrier.

Such topical composition may be used for the treatment of wounds including burns and ulcers especially decubitus ulcers (pressure sores).

EXAMPLES

The Examples which follow are set forth to aid in understanding the invention but are not intended to, and should not be construed to, limit its scope in any way.

Example 1

The Effect of Oxandrolone on Post-burn Catabolism (I)

A study on the effect of oxandrolone on post-burn patients was performed as described below.

Patient characteristics

Patients included in the study had a deep burn of 30–50% of body surface.

The patients included in this study had undergone:

a. catabolic phase until 80–90% of wound closure (4–10 weeks);

b. loss of 15–25% body weight (mostly lean body mass) during catabolic phase despite optimum nutrition;

The recovery of anabolic phase usually last 8–16 weeks with peak anabolism in the first 8 weeks.

The transition from "catabolic" to recovery "anabolic" was defined by:

a. No need for life support measures, being stable and out of the Intensive Care Unit (ICU);

b. No active infection (stress);

c. Open wound (not counting donor sites) not exceeding 10% Total Body Surface (TBS);

d. Patient taking oral diet with supplements or tube feeding (off parenteral feeding);

e. patient can actively participate in a physical therapy program with active ROM exercises accentuating the anabolic stimulus of exercise.

All patients were located in the burn step-down unit or in an acute rehabilitation hospital where daily information is retrieved from the physiatrist, nutritionist, and therapist.

The patients were divided into three groups in a prospective randomized manner:

Group 1: Standard nutritional goals as defined by the nutrition support service.

Group 2: Same as Group 1 plus 2–3 Met-Rx™ (protein supplement) per day (sufficient protein to increase daily protein intake to 2–2.2 g/kg/day).

Group 3: Same as Group 2 plus oxandrolone 20 mg orally four times daily.

Measurements

The following factors were checked:

a. Subjective energy level (per Braintree study) 0–10;

b. Physical therapy index[1] (per Braintree study) 0–10:

0	completes 25% session with fatigue
2	completes 50% session with fatigue
4	completes 75% session with fatigue
6	completes 100% session with fatigue
8	completes 100% session with no fatigue
10	completes 100% session and more with fatigue;

[1]assessment of muscle strength and endurance

c. Weekly weight gain;

d. Daily nutritional profiles;

e. Measurement of lean body mass by bioelective impedance.

The onset of the study was defined as the onset of the recovery phase (anabolic phase). Patients were studied for 3 weeks (from the onset of anabolism).

Results

The results are shown in FIGS. 1–6 and are described below:

1. The response to the catabolic phase was an 18% body weight loss despite optimum nutrition. The predicted amount of muscle loss is 70% of total loss since 4 lbs muscle are lost for 1 lb of fat.
2. The subjective energy level at the end of catabolism was 1–2 as expected.
3. Calorie and protein intake:

Group I

(10 patients): Despite high calorie, high protein diets and supplements or tube feedings, the calorie intake was below 25 cal/kg and protein intake below 1.5 g/kg protein. Patients were generally anorexic, felt full and did not like the supplements. Energy level and therapy index remained low for three weeks.

Group II

(7 patients): All patients liked the Met-Rx™ and actually ate better overall. Non-protein caloric intake improved slightly but significantly while protein intake doubled. Subjective energy level and quality of therapy were markedly increased and weight gain was double that of Group I unaccountable by the modest increase in calories alone.

Group III

(4 patients): Nutritional profile was comparable to Group II with an apparent added stimulus to food intake. Weight gain was four times that of Group I and energy level and therapy markedly improved.

Thus, increased protein intake in the form of Met-Rx™ markedly improved the rate of functional return in the recovery period. Attempt at improving nutrition with other standard nutrients was unsuccessful. The combination of Met-Rx™ and oxandrolone results in a great weight gain considered to be 80% lean body weight gain by bioelective impedance measurements.

Example 2

The Effect of Oxandrolone on Post-burn Catabolism (II)

Another study on the effect of oxandrolone on post-burn patients was carried out as follows.

Patient characteristics

Patients included in the study had a deep burn of 30–50% of body surface, reached recovery phase in about 4–6 weeks post-burn and required hospitalization for at least 3 weeks during the recovery phase.

The onset of the study was defined as the onset of the recovery phase (anabolic phase). The study period included the first three weeks of the recovery phase. Although somewhat arbitrary, the beginning of the recovery period was determined for all patients using the following criteria:

a. No need for life support measures, with a stable cardiopulmonary status;

b. No active infection;

c. Basal body temperature below 99.5° F.;

d. Metabolic rate at rest (indirect calorimetry) being less than 130% of normal;

e. Open wound (not counting donor sites) not exceeding 10% TBS;

f. Patient taking adequate oral diet with supplements or tube feeding and off all parenteral feeding;

g. active participation in a physical therapy program including resistance exercises especially to large muscle groups.

The patients were divided into three groups in a prospective randomized manner:

Group 1: High protein high calorie ad lib oral diet and protein supplement Met-Rx™. The supplement was given in a quantity equal to approximately one liter so that total protein intake would approximate 2 g/kg/day.

Group 2: Same as Group I with the addition of oxandrolone 10 mg orally twice a day.

Group 3: ad lib oral diet and a protein hydrolysate supplement (Ensure-HN or Sustacal). These is supplements contain approximately 40–45 g/l protein, 140–150 g/l carbohydrate and 30–37 g/l fat. Daily protein intake consumed equalled 1.3–1.5 g/kg or 75% above the RDA value for healthy normals of 0.8 g/kg. This group was managed in the ten months prior to the onset of this study.

All patients were located in the burn/trauma step-down unit and then transferred to an acute rehabilitation hospital usually within the first week of onset of the recovery period. A burn nurse coordinator followed all patients at the rehabilitation hospitals. All patients were monitored until discharge but only the first three week period was used for the study period.

Measurements

The following factors were checked:

a. Fatigue was measured objectively through increases in pulse of over 75% of predicted maximum (based on age) and a respiratory rate exceeding 30 breaths per minute beyond one minute after completion of the activity.

b. Muscle function was quantitated using a physical therapy index. The physical therapy program was determined for each patient by the burn therapist team based on optimum projected goals to be achieved at the three week period. Standard isokinetic and resistance exercises were used to increase strength. Ambulation, stair climbing and the stationary bike were used to increase endurance. Since the basic components of therapy programs were nearly identical between patients, an index was developed which quantitated progress of patient performance:

0	completes 25% session with fatigue
2	completes 50% session with fatigue
4	completes 75% session with fatigue
6	completes 100% session with fatigue
8	completes 100% session with no fatigue
10	completes 100% session and more with no fatigue;

c. Body weight;

d. Daily nutritional profiles;

e. Liver function

Within each group, paired data was analyzed using Dunnett's T-test comparing individual time periods. Between groups, analysis was compared by use of a nonparametric method, the Wilcoxan Signed Rank Test. Standard regression analysis was also performed. A $p<0.05$ was considered significant.

Results

The results are shown in FIGS. 7–9 and are described below:

All patients survived and have since been discharged to home. Groups 1 and 2 were evenly matched as to age, size of injury, period in the catabolic phase and weight loss. Group 1 had six patients, four males and two females. Group 2 had seven patients, four males and three females. Three patients in each group had a significant inhalation injury requiring initial ventilatory support in excess of two weeks. Weight loss in these patients did not exceed that for the group as a whole. Weight loss averaged 10–12% of reported pre-burn weight in both Group 1 and 2. An unknown portion of the weight loss was likely due to loss of tissue from wound excision as all patients had at least four excisions and graftings, 50% of procedures being excisions to fascia. Once the transition to the recovery phase was defined, no patient developed a significant infection or other acute process which would re-initiate the stress response.

Nutritional Profile

Mean data±standard deviation is shown in FIG. 7. Caloric intake was almost identical between all groups. Compliance with the supplement (MET-Rx) was >90% as the product flavor and texture could be adjusted depending on patient preference. Protein intake was identical in both Groups 1 and 2 being 2.0–2.2 g/kg/day as designed, compared to retrospective Group 3 who were given a high calorie, protein diet with standard supplements with a protein content which equalled 1.3–1.4 g/kg.

Liver Function Tests

One patient in both groups had a transient increase in alkaline phosphatase which resolved spontaneously.

Weight Gain

There was 2.5 to 3 pound weight gain in Group 1 per week, consistently over the three week study period (FIG. 8). In Group 2 weight gain over the three week period was double that of Group 1, a statistically significant difference. Weight gain was significantly increased in both Groups 1 and 2 over the retrospective Group 3.

Physical Therapy Index

In Group 1, the therapy index, a measure of muscle strength and endurance, increased rapidly and most patients were able to compete the entire expected program by the three week period without fatigue (FIG. 9). In Group 2, performance exceeded expectations, especially by week three. Expectations were in large part based on the standard gains in severe burns of this size in the early recovery phase previously managed. Both Groups 1 and 2 showed a significant increase in function over Group 3 at weeks two and three with Group 2 being significantly higher than either of the other groups.

Discharge Time

Average time of discharge from the rehabilitation or recovery phase to home for Group 1 was 26±5 days and Group 2 was 22±4 days while in Group 3 length of stay was 35±7 days. The average patient length of stay in the burn center was 25 days indicating the rapid wound closure and transfer to the rehabilitation center.

SUMMARY

A doubling of weight gain was noted in Group 1 using the protein hydrolysate MET-Rx for the same calorie intake compared to retrospective Group 3 and a marked improvement in muscle function. The biologic value of the added protein is reported to be greater than 95% by the manufacturer (MET-Rx, US, Inc., Irvine Calif.). This value indicates the percent of nitrogen in the hydrolysate retained by the body. Most available supplements use casein as the major protein. Casein has a biologic value of 60–70%. The addition of approximately 74 more grams of protein a day would not explain this doubling of weight unless all the added protein was used for muscle synthesis, a response only expected with an added anabolic stimulus. However, recent data on protein hydrolysate would indicate that biologic

properties of a protein hydrolysate exceed that of the contained nitrogen and that bioactive peptides produced by hydrolysis are absorbed intact and can increase anabolism and wound healing. Most of these peptides remain uncharacterized. If all the protein were converted to fat, this would result in only one half a pound of weight gain a week. Therefore, most of the 2.5 pound weight gain would need to be fat free or lean tissue. Correlation with increased strength also indicates the weight to be mostly muscle.

The addition of oxandrolone to the increased protein intake resulted in a marked increase in weight nearly four times that of retrospective Group 3 which at the time were ideally nutritionally managed. Rate of restoration of muscle function was also significantly increased in the oxandrolone group over protein alone. This rate of weight gain is likely muscle mass as opposed to fat since non-protein calorie intake was the same for both Groups 1 and 3. In addition, strength increased and discharge time decreased although the latter may not be a sensitive indication. Anabolic agents are known to markedly increase the efficiency of protein synthesis especially in muscle. Since one pound of muscle is 100 grams of protein and the rest is water, muscle weight gains can occur rapidly when the efficiency of anabolism is accentuated. Weight gain due to water retention is feasible, however water retention is not reported to occur with oxandrolone in doses below 80 mg.

In addition, 3 of 6 patients were followed for eight weeks after discontinuation of three weeks of oxandrolone and the weight remained. No hirsutism has been seen in the three women in the group and a transient small increase in alkaline phosphatase in one patient was the only chemical abnormality noted. This patient also had gallstones and the role of oxandrolone is questionable. Since the gain of muscle over and above normal body composition by body builders using anabolic agents diminishes with discontinuation of the drug the finding of maintenance of weight is important.

In summary, the rate of weight gain and muscle function can be significantly increased in the recovery phase after major burn using the anabolic steroid oxandrolone in combination with a high protein intake including a protein hydrolysate. This data indicates that manipulation of the recovery phase to shorten disability time is very feasible and that endogenous anabolic activity can be markedly increased.

Example 3

Oxandrolone Treatment of Patients Suffering from Pressure Sores

A paraplegic patient was suffering from pressure sores (decubitus ulcers) which had been unhealed for over one year. This patient was treated with oxandrolone (20 mg per day orally) and the sores began to heal. This preliminary result demonstrates that oxandrolone treatment promoted wound healing in decubitus ulcers of long duration. Further experiments using oxandrolone for treatment of pressure sores and other wounds are planned.

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What is claimed is:

1. A method of treating a skin wound in a patient suffering from the skin wound which comprises administering orally or topically a therapeutically effective amount of oxandrolone to the patient, wherein the skin wound is selected from the group consisting of a burn, an ulcer and a skin graft.

2. A method according to claim 1, wherein the skin wound is an ulcer.

3. A method according to claim 2, wherein the ulcer is a decubitus ulcer or a diabetic ulcer.

4. A method according to claim 1, wherein the skin wound comprises a skin graft.

5. A method according to claim 1 wherein the amount of oxandrolone is about 1–100 mg per day.

6. A method according to claim 5 wherein the amount of oxandrolone is about 20 mg per day.

7. A method according to claim 5 wherein the amount of oxandrolone is about 80 mg per day.

8. A method according to claim 1 wherein oxandrolone is in a solid dosage form.

9. A method according to claim 1 wherein oxandrolone is in a liquid dosage form.

10. A method according to claim 1 wherein oxandrolone is in a sustained-release formulation.

11. A method according to claim 1, wherein the skin wound is a burn.

12. A method of treating burn-induced weight loss in a burn patient which comprises administering orally or topically a therapeutically effective amount of oxandrolone in conjunction with a protein supplement to the patient.

13. A method according to claim 12 wherein the amount of oxandrolone is about 1–100 mg per day.

14. A method according to claim 12 wherein the amount of oxandrolone is about 20 mg per day.

15. A method according to claim 12 wherein the amount of oxandrolone is about 80 mg per day.

16. A method according to claim 12 wherein oxandrolone is administered orally.

17. A method according to claim 12 wherein oxandrolone is administered topically.

18. A method according to claim 12 wherein oxandrolone is in a solid dosage form.

19. A method according to claim 12 wherein oxandrolone is in a liquid dosage form.

20. A method according to claim 12 wherein oxandrolone is in a sustained-release formulation.

* * * * *

EXHIBIT D

US006670351B1

(12) **United States Patent**
Berger

(10) **Patent No.: US 6,670,351 B1**
(45) **Date of Patent: *Dec. 30, 2003**

(54) **METHOD FOR AMELIORATING MUSCLE WEAKNESS/WASTING IN A PATIENT INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS-TYPE 1**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(63) Continuation of application No. 08/244,988, filed as application No. PCT/US93/10063 on Oct. 20, 1993, now Pat. No. 6,090,799, which is a continuation-in-part of application No. 07/963,469, filed on Oct. 20, 1992, now abandoned.

(51) **Int. Cl.**[7] **A61K 31/56**
(52) **U.S. Cl.** **514/179**
(58) **Field of Search** 514/179

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(57) **ABSTRACT**

A method for attenuating the HIV-associated myopathy and muscle wasting associated with infection by human immunodeficiency virus-Type 1. Administration of oxandrolone in a daily dosage of about 2.5 to about 20 milligrams is described.

36 Claims, No Drawings

METHOD FOR AMELIORATING MUSCLE WEAKNESS/WASTING IN A PATIENT INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS-TYPE 1

This is a continuation of application U.S. Ser. No. 08/244,988, filed Jun. 22, 1995 now U.S. Pat. No. 6,090,799, now allowed, which is a §371 of PCT International Application No PCT/US93/10063, filed Oct. 20, 1993, which is a continuation-in-part of U.S. Ser. No. 07/963,469, filed Oct. 20, 1992 now abandoned.

TECHNICAL FIELD

The invention relates to the use of oxandrolone to attenuate myopathy and muscle weakness/wasting associated with infection by human immunodeficiency virus-Type 1.

BACKGROUND OF THE INVENTION

Human immunodeficiency virus (HIV) associated myopathy and/or muscle weakness/wasting is a relatively common clinical manifestation of acquired immunodeficiency syndrome (AIDS). This is one of a number of neuromuscular disorders associated with the disease. There is some evidence to indicate that direct HIV infection of muscle may be at least partly responsible, occasionally resulting in a polymyositis-like disorder. In addition, zidovudine (AZT), an antiviral agent that is used widely in the clinical management of AIDS, has been associated with a toxic myopathy, presumably related to an inhibition of mitochondrial metabolism. In any event, the loss of muscle mass commonly observed in AIDS victims negatively impacts muscle function, however caused.

Individuals with HIV-associated myopathy or muscle weakness or wasting typically experience significant weight loss, generalized or proximal muscle weakness, tenderness, and muscle atrophy. Laboratory tests of samples from such individuals often reveal elevated levels of enzymes associated with muscle degeneration and necrosis, such as creatine kinase, aldolase, and aspartate amino transferase. Electromyographic test results for individuals with HIV-associated myopathy are typically consistent with myopathic changes. Histopathologic tests may reveal muscle fiber necrosis associated with lymphocytic inflammatory infiltrates. In AZT myotoxicity, ragged red fibers are often observed.

Clinical management of HIV-associated myopathy and muscle weakness/muscle wasting varies. In individuals with AZT myopathy, withdrawal of this anti-retroviral agent may be associated with temporary improvement in strength and muscle bulk. Corticosteroid therapy, such as the administration of prednisone, has been occasionally successful when inflammatory infiltrates have been detected in muscle. However, a potential drawback to this approach is that corticosteroids, because of their immunosuppressant activity, may be harmful to individuals with AIDS who are already dangerously immunosuppressed as a consequence of the HIV infection.

Furthermore, corticosteroid use itself is associated with myopathies and an increased susceptibility to infections. Plasmapheresis has also been used with some success, although at least one patient has experienced, despite an increase in muscle strength, substantial weakness over a period of several weeks.

SUMMARY OF THE INVENTION

The present invention provides a method which employs oxandrolone (an anabolic steroid with weak androgenic activity) as an alternative approach to the clinical management of HIV-associated myopathy/muscle weakness/muscle wasting. Loss in muscle mass (wasting) is attenuated, and body weight can be more readily maintained in this manner. Such an approach has been applied successfully to improve strength, reverse weight loss, and provide an improved sense of well-being. Importantly, no evidence of liver injury or other untoward side effects have been observed.

Oxandrolone preferably is administered orally; however, other routes or administration can be utilized as well.

The present method of ameliorating muscle weakness or muscle wasting in a patient infected with HIV-1 comprises administering to the patient daily a sufficient amount of oxandrolone to attenuate the patient's rate of muscle mass loss. To this end, oxandrolone may be administered, orally or otherwise, in a daily dose in the range of about 2.5 to about 20 milligrams. However, the response of individual patients may vary and in some instances a daily dose greater than 20 mg may be required to achieve the desired response. The daily dose may be divided into unit doses of about 1 to about 5 milligrams each, administered to the patient three times per day at about eight-hour intervals.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Oxandrolone (17-hydroxy-17-methyl-2-oxaandrostan-3-one) is a known compound that is commercially available. The preparation of oxandrolone is described, inter alia, in U.S. Pat. No. 3,128,283 to Pappo, which description is incorporated herein by reference.

Pharmacologically, oxandrolone is a synthetic anabolic steroid similar in structure to testosterone, but having a different, lesser androgenic/anabolic activity ratio. In addition, oxandrolone is unique among all other testosterone analogues in that it contains an oxygen atom instead of a methylene group at the 2-position of the phenanthrene nucleus. In addition, oxandrolone lacks a 4-ene function in its A-ring. The anabolic potency of oxandrolone, estimated as approximately 3 to 13 times that of testosterone, 's believed to result form this unique structure.

Oxandrolone disposition and metabolism in man has been studied following oral administration of a 10 milligram dose. The study indicated that oxandrolone was rapidly and completely absorbed, yielding a mean peak plasma concentration of 417 micrograms of oxandrolone per milliliter at 66 minutes The plasma concentration of oxandrolone declined in a biphasic manner with a distribution half-life of approximately 30 minutes and an elimination half-life of 9.4 hours. Protein binding of oxandrolone was observed to be extensive.

In distinct contrast to other anabolic androgenic steroids such as methyltestosterone, fluoxymesterone, and micronized testosterone, oxandrolone taken orally is excreted mainly unchanged and unconjugated in urine. Urinary excretion of approximately 35 percent of an oral oxandrolone dose has been observed within 72 hours after ingestion. After 96 hours, approximately 65 percent of the administered oxandrolone dose was excreted in urine. Fecal excretion accounts for less than about 3 percent over the same time period.

Oxandrolone compositions, upon administration in accordance with this invention, ameliorate myopathy and muscle weakness in patients suffering from infections by human immunodeficiency virus-Type 1. Anabolic steroids, as a class, are known to stimulate appetite. Improved nutrition is important to individuals with AIDS who have experienced

loss of lean body mass. Further, as a consequence of direct interaction with androgen and/or glucocorticoid receptors in muscle, anabolic steroids promote muscle anabolism through both anabolic pathways and anticatabolic pathways.

Anabolic steroids, such as oxandrolone, also increase protein synthesis. For example, oxandrolone increased muscle protein synthesis in a study of acute uremic rats. Similarly, administration of oxandrolone preceded clinical improvement in appetite, cell mass, linear growth, and weight for height in sovs with chronic renal failure. These observations are consistent with anabolic activity. Oxandrolone may also stimulate the secretion of growth hormone and insulin-like growth factors.

In addition to producing beneficial direct anabolic action, oxandrolone is also believed to act as a delayed immunostimulant. In contrast, other appetite stimulants, such as dronabinol, that are currently under evaluation as appetite stimulants for AIDS patients can act as immunosuppressants in animals.

For purposes of administration in accordance with this invention, the active ingredient oxandrolone is combined with solid or liquid pharmaceutical carriers and formulated in unit dosage form using pharmacologically acceptable excipients, or dissolved or suspended in physiologically acceptable solvents or liquid vehicles for oral, percutaneous, or topical administration.

The overall daily dose of oxandrolone to provide a therapeutically effective amount in accordance with the method of this invention can be as low as about 2.5 milligrams and as high as about 20 milligrams, depending upon the patient's response and the mode of administration.

The amount of the active ingredient within the aforementioned ranges that is to be administered depends upon the age, weight and condition of the patient, as well as on factors such as the frequency and route of administration. In formulating oxandrolone, it is recognized that there may be differences between the immediate and the long term response. To account for these changes, the specific dosage given to a particular patient is based also on the individual patient's response. Preferably, oxandrolone is orally administered to the patient daily for a time period in the range of about 2 weeks to about 6 months.

Attenuation of the rate of muscle mass loss in a patient can be ascertained by comparing the patient's rate of weight loss before oxandrolone therapy with that after the administration of oxandrolone has been commenced. Alternatively, or in addition, the patient's urinary nitrogen level can be monitored, a well-known expedient. A decrease in the patient's urinary nitrogen level is indicative of a decrease in muscle mass loss.

Similarly, the maintenance of a relatively stable patient's total body potassium level, as well as an increase in the patient's total body potassium level, upon oxandrolone administration indicates that a therapeutically effective amount of oxandrolone is being administered. A patient's total body potassium level can be monitored, for example, as described in Kotler et al., The American Journal of Clinical Nutrition, 42:1255–1265 (December 1985) and Pierson, Jr., et al., Am. J. Physiol., 246 (Renal Fluid Electrolyte Physiol. 15:F234–F239 (1984).

The route of administration can be oral, percutaneous, transdermal, sublingual, buccal, intravenous, intramuscular, or the like. Of these, oral administration is preferred. The patient's daily dose of the active ingredient preferably is in the range of about 7.5 milligrams, but may exceed 20 milligrams based on clinical response. This daily dose can be given in tablet form as a single dose, or as plural divided doses, preferably 2 to 3 divided doses. The requisite daily dose can also be supplied continuously, for example, by a transdermal patch worn by the patient or intravenously. If the oxandrolone is administered orally, dosages in the range of about 2 to about 5 milligrams three to four times daily typically may be utilized.

Oxandrolone tablets are manufactured using standard solid dose form technology in accordance with United States Pharmacopeia (USP) specifications (see, for example, The United States Pharmacopeia, 22nd Revision, pp. 981–982). Specifically, a typical 150 milligram tablet contains the following:

Oxandrolone, USP	2.5 mg
Corn Starch, NF	30.0 mg
Lactose NF (hydrous)	113.0 mg
Hydroxypropyl Methylcellulose, USP	3.0 mg
Magnesium Steamte	1.5 mg
	150.0 mg

The terms "unit dosage form" and "unit dose" as used in the present specification and claims refer to a physically discrete unit or units suitable as unitary doses for patients, each unit containing a predetermined quantity of the active ingredient calculated to produce the desired therapeutic effect in association with the pharmacologically acceptable carrier. The specifications for the unit dosage forms of this invention are dictated in part and are also dependent upon (a) the unique characteristics of the active ingredient and (b) the particular therapeutic effect to be achieved, as well as upon limitations inherent in the art of compounding such active ingredient for the therapeutic use disclosed in detail in this specification. Examples of suitable unit dosage forms in accordance with this invention are tablets, pills, powder packets, wafers, cachets, segregated multiples of any of the foregoing, transdermal patches, alicaots of injectables, and the like forms.

The primary response variables are patient's total body potassium, body weight, muscle mass, muscle strength, improvement in or increased appetite, and general sense of well-being. In addition, improvement in immune status (or at a minimum, no worsening of immune function) in response to oxandrolone is significant as well.

An important question regarding the use of any drug in combination with anti-retroviral therapy is whether drug interactions may occur that would diminish AZT efficacy or increase the frequency of severity of AZT-related adverse reactions. TABLE 1 compares various published pharmacological parameters for oxandrolone and AZT and illustrates important differences between the two drugs.

TABLE 1

Comparison of Selected Oxandrolone and AZT Pharmacology Parameters

Parameter	Oxandrolone	AZT
Oral Bioavailability	100%	65%
Tmax	1.1 hr	0.7 hr
Biological T½	9.4 hr	1.1 hr
Vd	578 ml/kg	>1400 ml/kg
Protein Binding	>95%	25–35%
Plasma Clearance	43 ml/kg/hr	>1300 ml/kg/hr

TABLE 1-continued

Comparison of Selected Oxandrolone and AZT Pharmacology Parameters

Parameter	Oxandrolone	AZT
Metabolism	Little	Extensive
Glucuronidation	Little	Substantial
Urinary Excretion	Extensive; primarily parent compound	Extensive: parent and glucuronide conjugated
Target Organ Toxicity	Liver (anabolic steroids as class)	Hematopoietic system (e.g., anemia, granulocytopenia)
Known Drug Interactions	Anticoagulants; oral hypoglycemic agents; adrenal steroid when edema present	Drugs that may: (a) inhibit glucuronidation (e.g., aspirin, acetaminophen) or urinary excretion (e.g., probenecid); (b) adversely affect blood cell number and function; and (c) nephrotoxic or cytotoxic

Because oxandrolone is primarily protein bound, whereas AZT is primarily non-protein bound, oxandrolone will not compete appreciably with AZT for binding sites in plasma. Consequently, administration of oxandrolone to patients on AZT therapy is unlikely to alter the level of free AZT in the blood. Likewise, the administration of AZT is unlikely to alter the level of free oxandrolone in the blood. An oxandrolone-AZT drug interaction involving binding site displacement is, therefore, extremely unlikely.

AZT is rapidly metabolized and excreted in the urine—a significant quantity is excreted in the form of glucuronide conjugates. In sharp contrast, oxandrolone, perhaps due to presence of a lactone group and the absence of a 4-ene function in the A-ring, undergoes little hepatic metabolism and is excreted primarily unchanged and unconjugated in urine. Thus, in contradistinction to other drugs that may competitively inhibit glucuronidation and thereby potentially slow the rate of AZT metabolism, such as aspirin, acetaminophen, or indomethacin, the present active agent, oxandrolone, is not believed to affect AZT metabolism.

Furthermore, oxandrolone is neither nephrotoxic nor cytotoxic. Accordingly, oxandrolone is not expected to interfere with the renal excretion of AZT or its metabolites. To the contrary, oxandrolone has been safely and effectively used in patients with chronic renal disease to stimulate growth and increase lean body mass. In well-controlled studies of oxandrolone for the clinical management of critically ill patients with acute alcoholic hepatitis, oxandrolone administered at daily doses of up to 80 mg/day for four weeks and 40 mg/day for eight weeks did not result in any drug-related nephrotoxicity.

While it is known that anabolic androgenic steroids have been associated with potentially life-threatening forms of liver disease, including peliosis hepatis, cholestatic jaundice, and hepatocellular neoplasms, specific reports in the medical literature regarding liver disease in oxandrolone-treated patients at the dosages proposed for use in the clinical management of HIV associated muscle weakness/wasting (i.e., about 2.5 to about 20 mg/day) are rare.

Oxandrolone and AZT have different mechanisms of action. They also function in different sites of cellular action at the receptor level. Oxandrolone functions via interaction with androgen and glucocorticoid receptors, whereas AZT, once phosphorylated, acts to inhibit HIV reverse transcription. Thus, competitive inhibition of AZT by oxandrolone at the cellular level also is considered unlikely.

Neither has oxandrolone been associated with anemia or granulocytopenia, two frequently occurring and potentially serious side effects associated with AZT therapy. To the contrary, anabolic androgenic steroid have been used clinically to stimulate ethyropoiesis in hypoanemias, aplastic anemias, hemalytic anemias, renal anemias, anemias due to cytotoxic therapy, and various leukemias. It has been reported recently that androgens augment beneficial effects of erythropoietin in the treatment of anemia resulting from end-stage renal disease.

Data derived from animal models and human clinical studies indicate that anabolic steroids are unlikely to suppress immune function in patients infected with HIV. For example, anabolic steroids can stimulate granulopoiesis in mice, as evidenced by stimulation of granulocytic colony-forming cells derived from spleen and bone marrow. Similarly, an anabolic steroid known as nandrolone decanonate enhanced macrophage activity and cell-mediated immunity in patients with uterine cervical cancer when administered parentally. In related studies, anabolic steroids increased peripheral lymphocyte and monocyte counts, Immunoglobin G (IgG) levels, and PHA-blastoid transformation of peripheral lymphocytes. In those studies, β_2-microglobulin levels simultaneously decreased.

IgG is one of a class of antibodies secreted by B cells (i.e., B-lymphocytes) in response to an antigenic challenge (e.g., foreign protein like that from bacteria). In the case of HIV infection, humoral immune function (i.e., B-cell mediated) is significantly impaired. Accordingly, when HIV-infected individuals are challenged with a specific antigen, the typical response of B-cell proliferation, differentiation and secretion of antibodies (e.g., IgG) is diminished or absent. This decline in humoral immune function coupled with defects in cellular immune (i.e., T-cell) function contributes to the overall failure of the immune system to respond in an appropriate manner to challenge. B-cells in AIDS victims are, by mechanisms unknown, hyperstimulated to secrete large amounts of immunoglobulins that make the humoral system refractor to new antigens. The result is that the patient's system no longer recognizes new antigens and does not respond.

In animal studies in which anabolic steroids have been reported to increase IgG and PHA-blastoid activity, these changes occurred as a result of immune system stimulation, and are positive responses. β-microglobin is a cell surface protein that is found on all nucleated cells and it is released into the serum during cell turnover. Generally, β-microglobulin is considered a marker of infectious, inflammatory, malignant and autoimmune disease activity. In several AIDS studies, β-microglobulin levels correlated with disease progression and T4 (T-helper) cell counts. In the case of therapy with oxandrolone, for example, a decrease in β-microglobulin levels is desirable. Thus, animal data showing reduced plasma levels of β-microglobulin in response to anabolic steroids is evidence of a positive effect and suggestive of similar activity in man.

Accordingly, there are no reasons to believe that the administration of an anabolic steroid in general and oxandrolone in particular would have adversed effects on the immune system. Generally, the target organ of toxicity for these drugs is the liver—probably because this is where most are metabolized. Oxandrolone, however, has a remarkably good safety profile in man as a likely consequence of its resistance to hepatic metabolism; an oral dose is excreted primarily in urine as the parent compound, as stated hereinabove.

Data from clinical trials in patients with severe alcoholic liver disease provide further evidence that oxandrolone is

not likely to suppress immune function in patients with HIV infection. Ethanol abuse is associated with loss of lymphocyte functions, particularly T-cell dependent immune responses. Previous researchers have observed that oxandrolone significantly improved lymphocyte number in patients with severe alcoholic hepatitis Because the loss of lymphocytic function by alcoholic liver disease parallels, to a significant degree, the loss of T-cell function due to HIV infection, it is reasonable to hypothesize that oxandrolone will increase the T-Cell function of HIV-infected patients.

Therefore, these data from laboratory animals and human studies indicate that suppression of the immune system by anabolic steroids, such as oxandrolone, is unlikely. Nonetheless, subjects undergoing oxandrolone therapy, as a precaution, should be monitored for changes in lymphocyte number, particularly CD4+ and CD8+, as is routinely done for patients who undergo steroid therapy.

In summary, based on the differences between AZT and oxandrolone with respect to pharmacokinetics, metabolism, reported drug interactions, mechanisms of action, and reported toxicities, oxandrolone and AZT can be safely used in combination for subjects infected with the Type-1 HIV virus and suffering from HIV-associated myopathy. The use of oxandrolone in patients on AZT therapy is, on the basis of known drug interactions, also consistent with current FDA-approved labeling for AZT and oxandrolone.

The following example demonstrates the effectiveness of oxandrolone in attenuating the effects of HIV-associated muscle weakness or muscle wasting in an AIDS patient.

EXAMPLE

A patient, a thirty-two year old homosexual man, known to be HIV-seropositive since February 1989, noted difficulty opening drawers and bottles in May 1989. The patient weakened progressively and, during a physical examination in September 1989, demonstrated by confrontation testing the weakness of neck flexion and proximal limbs. However, his muscle stretch reflexes remained normal. Laboratory tests showed the patient's creatine kinase level to be 286 International Units per liter, much higher than the normally observed range for creatine kinase of about 40–200 Units per liter.

Zidovudine (azidothymidine or AZT) was initiated at 500 milligrams daily, but the patient's strength continued to decline through February 1990. He complained of an inability to ascend a flight of stairs. The patient exhibited greater weakness and atrophy of neck flexors and extremity muscles during another physical examination performed at this time. An electromyogram revealed a decrease of amplitude and duration of the patient's motor unit potentials and increased recruitment in selected muscles of his right upper extremity. The patient's creatine kinase tested at 456 Units per liter. A muscle biopsy revealed numerous myofibers, abundant ragged red fibers, and numerous cosinophilic inclusions. Round cell inflammatory infiltrates were also noted. In light of these developments, the zidovudine treatment was terminated.

Substantial improvement initially followed the discontinuation of zidovudine. However, because of a subsequent continued and progressive weakness rendering it difficult for the patient to ascend or descend a flight of stairs, a prednisone therapy (60 mg daily) was initiated. No significant improvement accompanied the use of prednisone.

Thereafter, a trial period of oral oxandrolone administration (2.5 milligrams, three times daily, in tablet form) was initiated. Within two weeks of the initiation of the oxandrolone therapy, the patient noted an improved sense of well being, became stronger, and gained weight. Within one month, he was able to ascend and descend stairs without problems. Confrontation testing revealed nearly normal strength. The patient's weight increased from 115 pounds to 130 pounds. The patient's muscle atrophy was alleviated as well. Liver functions were closely monitored for signs of elevation, but undesirable side effects were not detected.

After several months of the aforementioned therapy with oxandrolone, the patient was no longer able to obtain oxandrolone for use as a medication. Weakness and weight loss ensued. Trials of other anabolic preparations, specifically stanazol and oxymethalone, did not return the patient to his previous levels of function and strength.

The EXAMPLE demonstrates that oxancrolone can be a beneficial alternative for clinical management of HIV-associated myopathy and muscle weakness and wasting.

It is intended that the foregoing description is by way of illustration only and is not to be construed as limiting the invention in any way except in the spirit and scope of the appended claims.

What is claimed is:

1. A method for ameliorating HIV-associated myopathy and muscle wasting in an AIDS patient which comprises administering a therapeutically effective amount of oxandrolone to the AIDS patient.

2. The method in accordance with claim 1 wherein the therapeutically effective amount comprises a daily dosage of between about 2.5 to about 30 milligrams.

3. The method in accordance with claim 1 wherein the therapeutically effective amount comprises a daily dosage of between about 2.5 to about 20 milligrams.

4. The method in accordance with claim 3 wherein the daily dosage is about 20 milligrams.

5. The method in accordance with claim 3 wherein the daily dosage is about 15 milligrams.

6. The method in accordance with claim 1 wherein the oxandrolone is administered orally.

7. The method in accordance with claim 6 wherein the oxandrolone is administered in the form of a tablet.

8. The method in accordance with claim 2 wherein the oxandrolone is administered orally.

9. The method in accordance with claim 8 wherein the oxandrolone is administered in the form of a tablet.

10. The method in accordance with claim 3 wherein the oxandrolone is administered orally.

11. The method in accordance with claim 10 wherein the oxandrolone is administered in the form of a tablet.

12. The method in accordance with claim 4 wherein the oxandrolone is administered orally.

13. The method in accordance with claim 12 wherein the oxandrolone is administered in the form of a tablet.

14. The method in accordance with claim 5 wherein the oxandrolone is administered orally.

15. The method in accordance with claim 14 wherein the oxandrolone is administered in the form of a tablet.

16. The method in accordance with claim 1 wherein the oxandrolone is administered daily for a time period in the range of about two weeks to about six months.

17. The method in accordance with claim 6 wherein the oxandrolone is administered daily for a time period in the range of about two weeks to about six months.

18. The method in accordance with claim 8 wherein the oxandrolone is administered daily for a time period in the range of about two weeks to about six months.

19. The method in accordance with claim 10 wherein the oxandrolone is administered daily for a time period in the range of about two weeks to about six months.

20. The method in accordance with claim 12 wherein the oxandrolone is administered daily for a time period in the range of about two weeks to about six months.

21. The method in accordance with claim 14 wherein the oxandrolone is administered daily for a time period in the range of about two weeks to about six months.

22. The method in accordance with claim 1 wherein the oxandrolone is administered percutaneously.

23. The method in accordance with claim 1 wherein the oxandrolone is administered intravenously.

24. The method in accordance with claim 1 wherein the oxandrolone is administered intramuscularly.

25. The method in accordance with claim 1 wherein the oxandrolone is administered sublingually.

26. The method in accordance with claim 1 wherein the oxandrolone is administered transdermally.

27. The method in accordance with claim 1 wherein the oxandrolone is administered in a unit dose of about 2 to about 5 milligrams three times daily.

28. The method in accordance with claim 2 wherein the oxandrolone is administered in a unit dose of about 2 to about 5 milligrams three times daily.

29. The method in accordance with claim 3 wherein the oxandrolone is administered in a unit dose of about 2 to about 5 milligrams three times daily.

30. The method in accordance with claim 4 wherein the oxandrolone is administered in a unit dose of about 2 to about 5 milligrams three times daily.

31. The method in accordance with claim 5 wherein the oxandrolone is administered in a unit dose of about 2 to about 5 milligrams three times daily.

32. The method in accordance with claim 1 wherein the oxandrolone is administered in a unit dose of about 1 to about 5 milligrams three or four times daily.

33. The method in accordance with claim 2 wherein the oxandrolone is administered in a unit dose of about 1 to about 5 milligrams three or four times daily.

34. The method in accordance with claim 3 wherein the oxandrolone is administered in a unit dose of about 1 to about 5 milligrams three or four times daily.

35. The method in accordance with claim 4 wherein the oxandrolone is administered in a unit dose of about 1 to about 5 milligrams three or four times daily.

36. The method in accordance with claim 5 wherein the oxandrolone is administered in a unit dose of about 1 to about 5 milligrams three or four times daily.

* * * * *

EXHIBIT E

US006828313B2

(12) **United States Patent**
Fishbein

(10) **Patent No.: US 6,828,313 B2**
(45) **Date of Patent: Dec. 7, 2004**

(54) **USE OF OXANDROLONE IN THE TREATMENT OF BURNS AND OTHER WOUNDS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/011,377**

(22) Filed: **Oct. 22, 2001**

(65) **Prior Publication Data**

US 2002/0165266 A1 Nov. 7, 2002

Related U.S. Application Data

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(51) **Int. Cl.**[7] **A61K 31/56**; A61K 31/58

(52) **U.S. Cl.** **514/171**; 514/2; 514/175; 514/179; 514/925; 514/928

(58) **Field of Search** 514/2, 171, 175, 514/179, 925, 928

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(57) **ABSTRACT**

The subject invention provides a method of treating burn-induced weight loss in a burn patient which comprises administering a therapeutically effective amount of an oxandrolone to the patient. The invention also provides a method of treating a wound in a patient suffering from a wound which comprises administering a therapeutically effective amount of an oxandrolone to the patient. The subject invention further provides a method of treating burn-induced weight loss in a burn patient which comprises administering a therapeutically effective amount of an oxandrolone in conjunction with a protein supplement to the patient.

33 Claims, 9 Drawing Sheets

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FIGURE 1

RESPONSE TO BURN INJURY, MET-Rx, OXANDRIN

	CATABOLIC PHASE					ANABOLIC PHASE						
	AGE	BURN % BSA	CATABOLIC PHASE (DAYS)	WEIGHT LOSS (LBS)	%TOTAL	ONSET	ENERGY LEVEL			THERAPY INDEX		
							1	2	3 (wks)	1	2	3 (wks)
ROUP 1 n=10)	25±9	35±9	38±9	30±5	18±3	1	2±1	2±1	3±2	2±1	3±1	3±1*
ROUP 2 MET-Rx n=7)	28±8	38±9	37±11	28±6	17±4	2	4±1*	6±2*	7±2*	3±1	6±1*	6±2*
ROUP 3 ET-Rx, xandrin n=4)	27±10	37±10	36±10	29±5	18±4	3	5±1*	8±2*	8±2*	4±1*	7±1*	8±2*

*significant difference between groups p<0.05

RESPONSE TO BURN INJURY, MET-Rx, OXANDRIN

	CATABOLIC PHASE NUTRITIONAL PROFILE					ANABOLIC PHASE					
	Cal+ kg/day	Prot g/kg/day	Cal/kg/day+			Prot/g/kg/day			Weight Gain (lbs)		
			1	2	3 (wks)	1	2	3 (wks)	1	2	3(wks)
GROUP 1 (n=10)	30±2	1.9±0.02	22±2	23±2	23±3	1.3±0.1	1.3±0.1	1.2±0.1	1.2±0.1	1.3±0.2	1.4±0.2
GROUP 2 (n=7)	31±3	2.0±0.2	24±3	27±2*	28±3*	2.0±0.2	2.1±0.1	2.2±0.2	2.5±0.2*	2.7±0.1*	2.9±0.2*
GROUP 3 (n=4)	31±3	1.9±0.1	25±2	28±2*	30±3*	2.1±0.1	2.1±0.1	2.2±0.1	4.9±0.5*	5.0±0.5*	5.1±0.5*

*significant difference between groups p<0.05
+non-protein calories

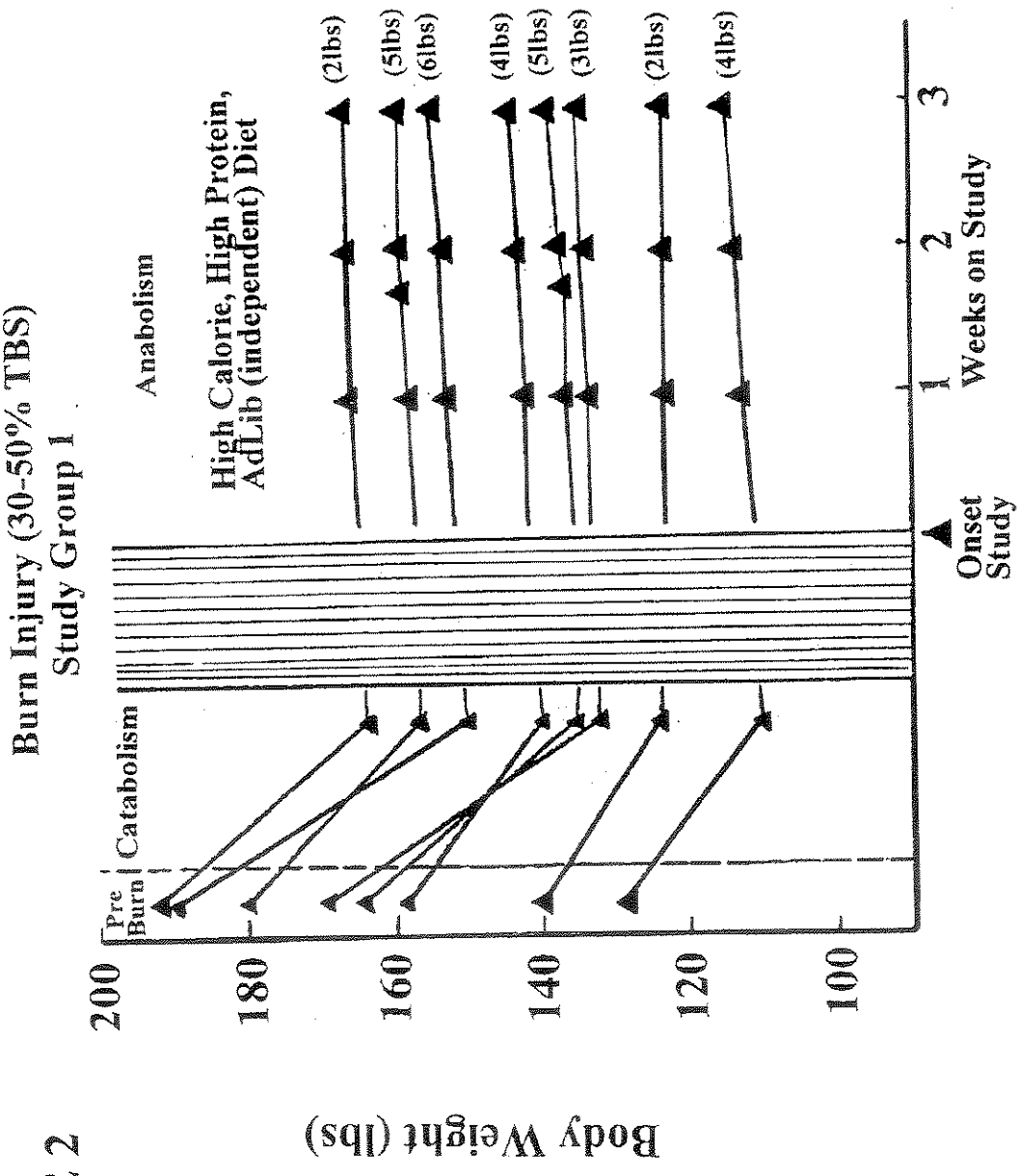
Burn Injury (30-50% TBS)
Study Group 1
Anabolism
Catabolism
Pre Burn
High Calorie, High Protein, AdLib (independent) Diet
(2lbs)
(5lbs)
(6lbs)
(4lbs)
(5lbs)
(3lbs)
(2lbs)
(4lbs)
Onset Study
Weeks on Study
Body Weight (lbs)
200
180
160
140
120
100
1
2
3

FIGURE 2

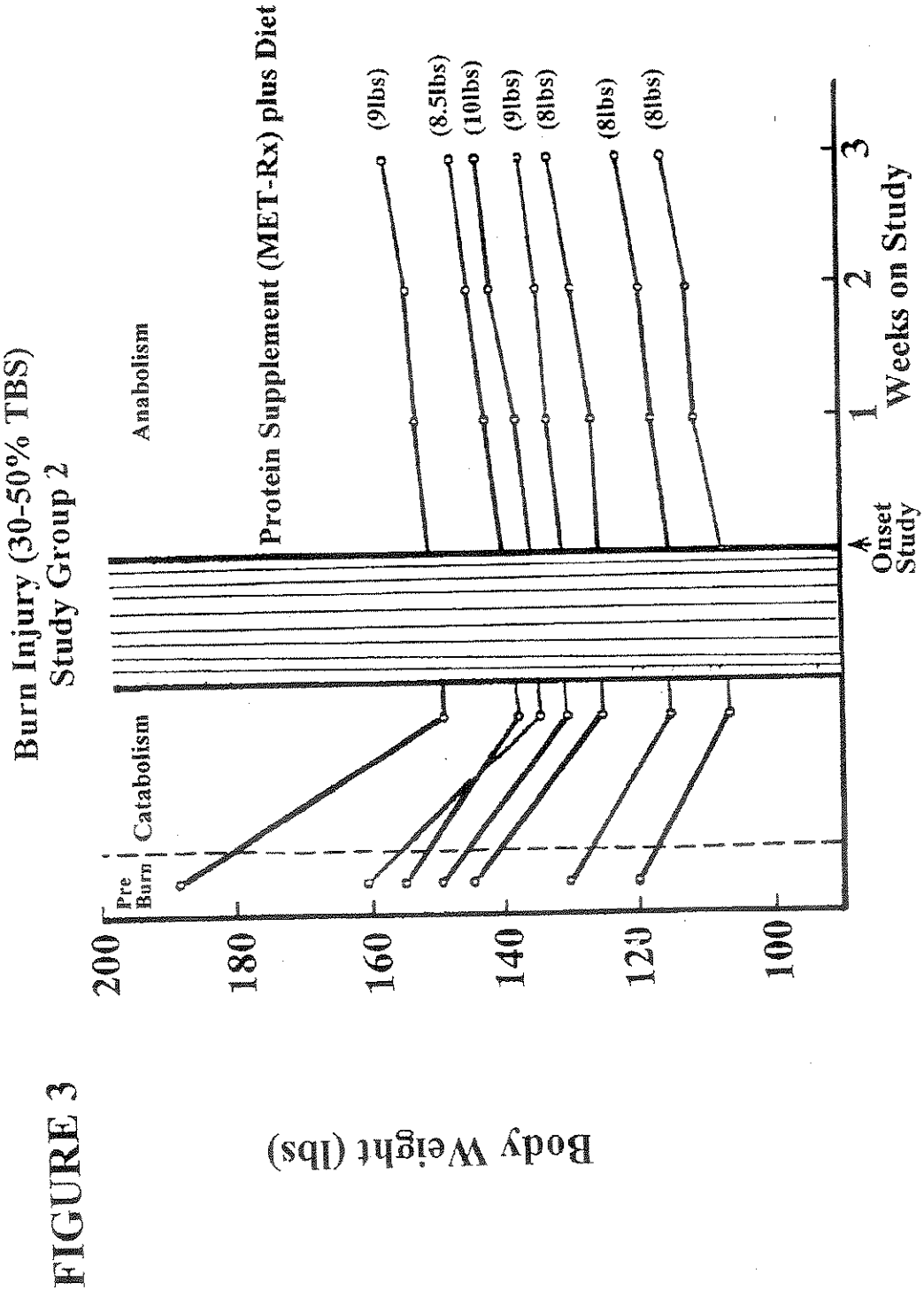
Burn Injury (30-50% TBS)
Study Group 2
Anabolism
Protein Supplement (MET-Rx) plus Diet
(9lbs)
(8.5lbs)
(10lbs)
(9lbs)
(8lbs)
(8lbs)
(8lbs)
Onset Study
1
2
3
Weeks on Study
Catabolism
Pre Burn
200
180
160
140
120
100
Body Weight (lbs)

FIGURE 3

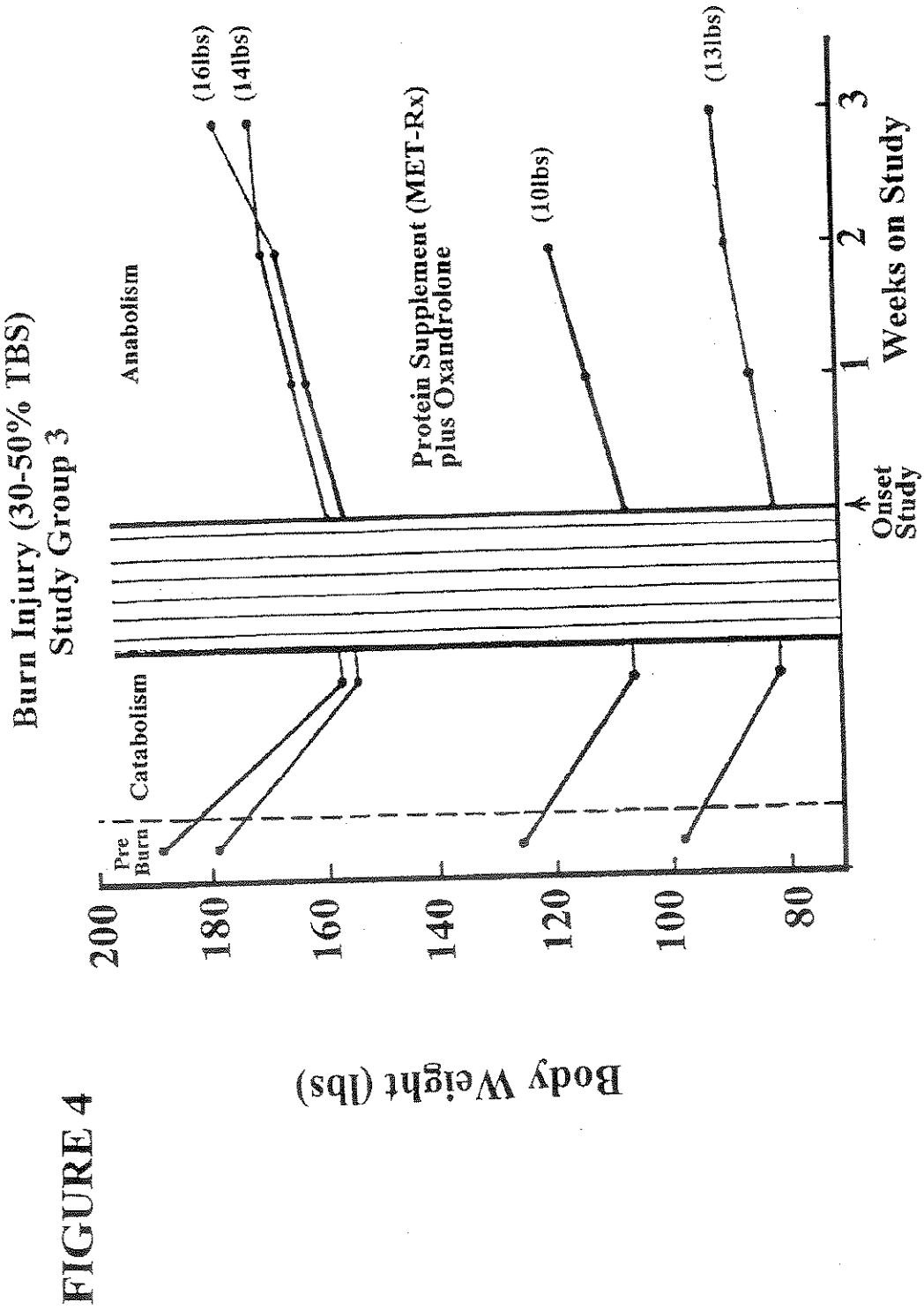
Burn Injury (30-50% TBS)
Study Group 3
Anabolism
Catabolism
Pre Burn
Protein Supplement (MET-Rx)
plus Oxandrolone
(16lbs)
(14lbs)
(10lbs)
(13lbs)
Onset Study
Weeks on Study
1
2
3
200
180
160
140
120
100
80
Body Weight (lbs)

FIGURE 4

FIGURE 5

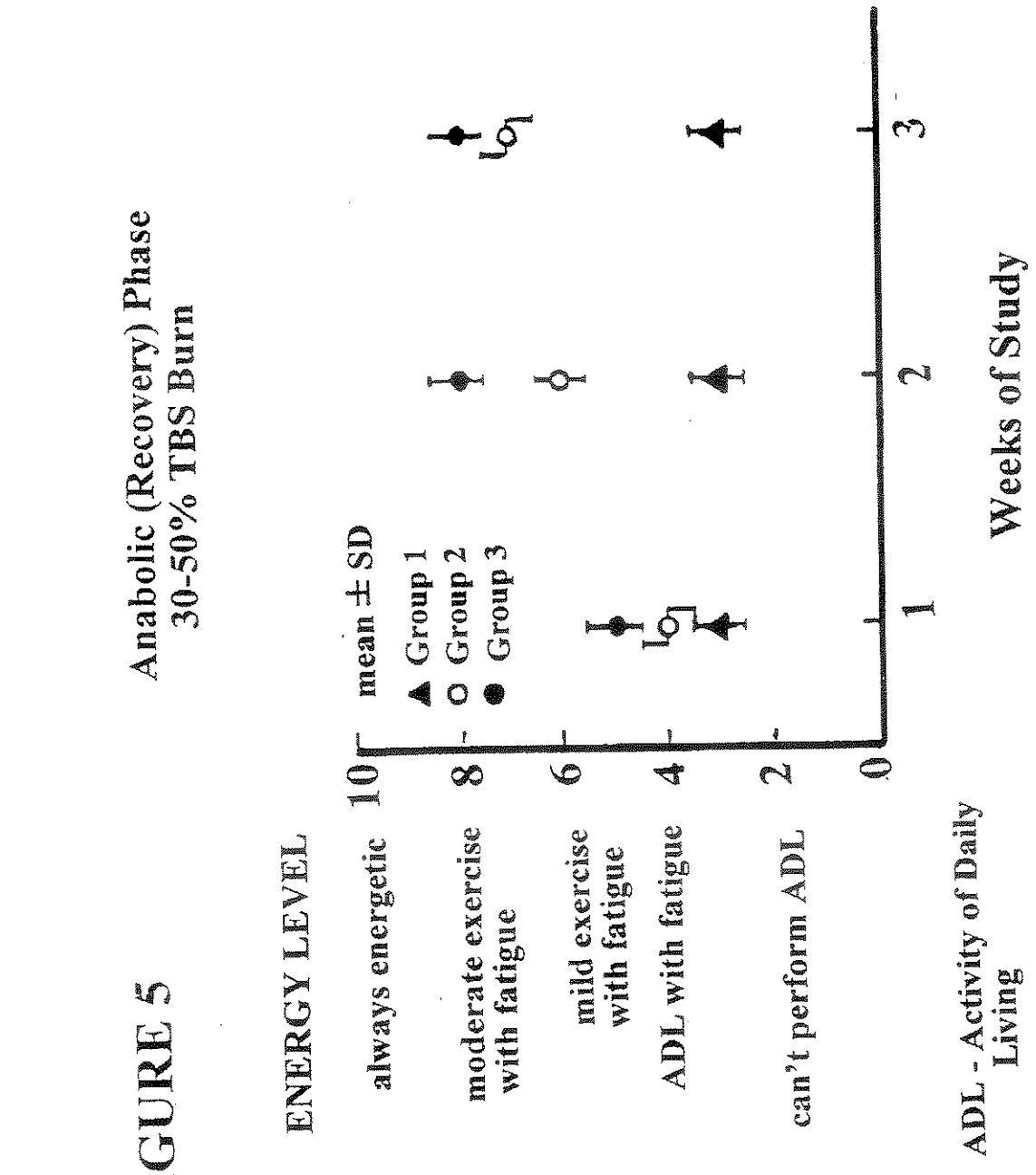
Anabolic (Recovery) Phase
30-50% TBS Burn
ENERGY LEVEL
always energetic
moderate exercise with fatigue
mild exercise with fatigue
ADL with fatigue
can't perform ADL
ADL - Activity of Daily Living
10
8
6
4
2
0
mean ± SD
Group 1
Group 2
Group 3
1
2
3
Weeks of Study

FIGURE 6

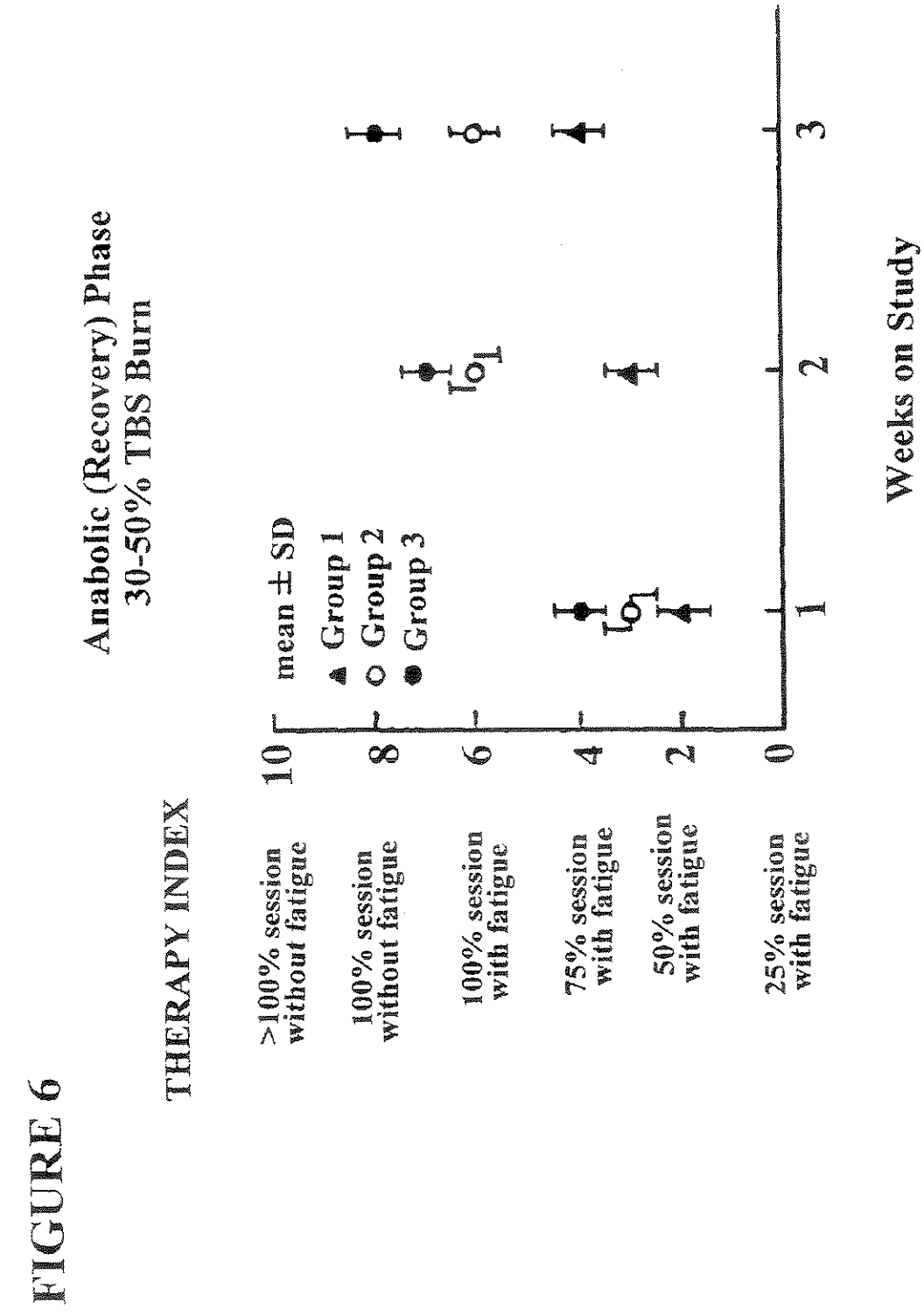
Anabolic (Recovery) Phase
30-50% TBS Burn
THERAPY INDEX
mean ± SD
Group 1
Group 2
Group 3
>100% session without fatigue
100% session without fatigue
100% session with fatigue
75% session with fatigue
50% session with fatigue
25% session with fatigue
10
8
6
4
2
0
1
2
3
Weeks on Study

FIGURE 7

EFFECT OF ANABOLIC AGENT AND INCREASED PROTEIN CONTENT ON THE RECOVERY PHASE

	CATABOLIC PHASE					RECOVERY (ANABOLIC) PHASE (WKS)								
						NUTRITIONAL PROFILE						WEIGHT GAIN		
						Cal/kg/day*			Prot/g//kg/day			Pounds Per Week		
	AGE	BURN %BSA	DAYS	WT. LOSS LBS.	%TOTAL	1	2	3	1	2	3	1	2	3
roup 1 (n=6)	34±8	45±8	39±9	20±7	12±4	32±4	34±4	35±5	1.9±0.1	2±0.2	2.2±0.1	2.5±0.2	2.6±0.4	2.6±0.5
roup 2 (n=7)	36±9	47±6	35±9	21±6	11±3	33±3	33±4	34±4	2.0±0.2	2.0±0.2	2.2±0.2	3.9±0.4*	4.4±0.5*	4.8±0.5*
roup 3 n=10)	39±8	42±7	32±10	19±8	11±6	34±3	33±3	33±5	1.5±0.2*	1.4±0.2*	1.4±0.3*	1.2±0.1*	1.3±0.2*	1.4±0.2*

nificant difference between groups 1 and 2 $p<0.05$
nificant difference between groups 1 and 3 $p<0.05$

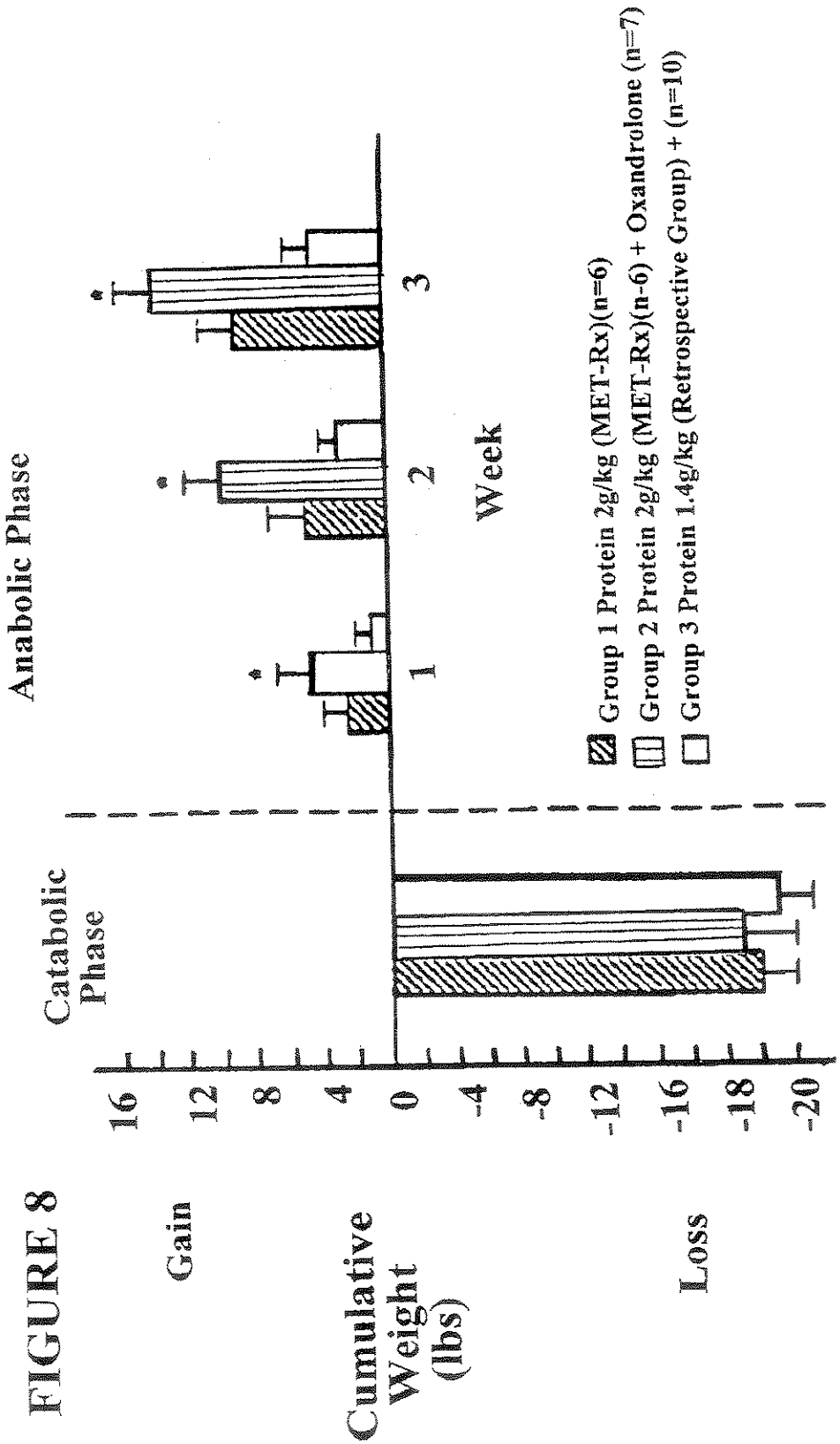
Anabolic Phase
Catabolic Phase
Week
1
2
3
Group 1 Protein 2g/kg (MET-Rx)(n=6)
Group 2 Protein 2g/kg (MET-Rx)(n-6) + Oxandrolone (n=7)
Group 3 Protein 1.4g/kg (Retrospective Group) + (n=10)
16
12
8
4
0
-4
-8
-12
-16
-18
-20
Gain
Loss
Cumulative Weight (lbs)

FIGURE 8