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(54) **METHOD OF ACHIEVING A THYMOSIN BETA 4 CONCENTRATION IN A HUMAN PATIENT**

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(57) **ABSTRACT**

The present invention provides embodiments which involve methods of providing a predetermined concentration of thymosin beta 4 (TB4) at a predetermined time, t, in a body portion of a live human patient. The methods can include determining a thymosin beta 4 treatment dosage (D) using Formula I: $C=(A)D.t^{-B}$, wherein C is the predetermined concentration at time t, in ng/mL, D is the dosage of thymosin beta 4 administered in mg, t is the time elapsed after administration of dosage D in hours, A is about 30 to about 38, and B is about 0.5 to about 1; and administering the dosage (D) of thymosin beta 4 to the patient. Formula I may be, for example,

$C=(35.6)D.t^{-0.754}$ (Formula II).

METHOD OF ACHIEVING A THYMOSIN BETA 4 CONCENTRATION IN A HUMAN PATIENT

BACKGROUND OF THE INVENTION

[0001] 1. Technical Field

[0002] The invention relates to the field of medicinal treatment and in particular to methods for providing a pharmaceutical dosage of thymosin beta 4 to a patient.

[0003] 2. Description of the Background Art

[0004] Thymosin beta 4 (TB4) initially was identified in the thymus. It is a 43-amino acid polypeptide, now known to exist in a number of tissues throughout the body. Several roles have been ascribed to this peptide, and it has been found to be useful in treating a number of conditions where immune modulation, endothelial cell differentiation and migration, T cell differentiation, actin sequestration or angiogenesis would be desirable. For example, TB4 has been used to accelerate wound healing. The amino acid sequence of TB4 is disclosed in U.S. Pat. No. 4,297,276, the disclosures of which are incorporated by reference herein.

[0005] Obtaining a desired concentration suitable for treatment is difficult when the half-life of TB4 is not great. In particular, dosage administration is not very effective in cases where the dose administered produces a high initial TB4 concentration of the drug which is far greater than the desired concentration and where the concentration rapidly decreases. Frequent re-dosing often is necessary, creating large swings in TB4 concentration. This results in both an inefficient treatment and the dangers inherent with fluctuating or unpredictable concentrations of an active compound.

SUMMARY OF THE INVENTION

[0006] In accordance with the present invention, a method of providing a desired concentration of administered thymosin beta 4 (TB4) in a body portion of a live human patient in need thereof, at a predetermined time t, is comprised of determining a thymosin beta 4 treatment dosage (D) using Formula I

$$C=(A)D.t^{-B} \quad \text{(Formula I)},$$

wherein C is the predetermined concentration at time t, in ng/mL, D is the dosage of thymosin beta 4 to be administered to the live human patient in mg, t is the time elapsed after administration of dosage D in hours, A is about 30 to about 38, and B is about 0.5 to about 1. The present invention further comprises administering the dosage (D) of thymosin beta 4 to the live human patient so as to achieve the desired concentration of administered thymosin beta 4 in the body portion.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

[0007] When a large dose of thymosin beta 4 (TB4) is administered to a patient, such that the concentration produced is higher than needed for treatment or efficient treatment, the drug may be degraded more quickly, may not be effectively used by the patient, may result in waste of TB4 or may possibly even result in unexpected side effects related to overdose. When the dose administered provides thymosin beta 4 concentrations that are too low for optimum efficiency, the patient may receive an inadequate dose and re-dosing may be required at frequent intervals, reducing compliance and effectiveness. An ideal dosing regimen consistently maintains thymosin beta 4 concentrations at a specific desired level or within a specific desired range which is effective to treat the patient, but which also minimizes the total amount of drug which is administered over the treatment period. There is a need in the art for improved methods to determine an effective dose of thymosin beta 4 in a patient which can avoid waste in the form of unnecessary over-administration and in the form of inadequate and ineffective under-administration.

[0008] Embodiments of the present invention provide a method of achieving a predetermined concentration of thymosin beta 4 in a body portion of a live human patient, e.g., a human patient in need of treatment. Certain embodiments of the present disclosure provide a method of achieving a predetermined fluid concentration of thymosin beta 4 in a fluid portion of a live human patient. Other embodiments include a method of achieving a predetermined liquid concentration of thymosin beta 4 in a liquid portion of a live human patient. In another embodiment, the present disclosure provides a method of achieving a predetermined blood concentration of thymosin beta 4 in a live human patient. In another embodiment, the present disclosure provides a method of achieving a predetermined plasma concentration of thymosin beta 4 in a live human patient. The ability to determine the dosage needed to achieve the desired concentration of thymosin beta 4 is advantageous because it provides an effective therapeutic benefit for the particular patient and also avoids the waste of an expensive biological product through over-dosing.

[0009] The term "patient" as used herein means any live human person to whom thymosin beta 4 can be administered.

[0010] The term "body portion" as used herein denotes any anatomical space, tissue or region of the body, including body fluids and secretions, and includes but is not limited to any natural or artificially created body cavity or space, for example: abdominal cavity, buccal cavity, cerebral cavity, gastric cavity, gingival space, intra-articular space, nasal cavity, oral cavity, pelvic cavity, pericardial space, peritoneal cavity, pleural cavity, subarachnoid space, subcutaneous space, urinary bladder cavity, uterine cavity, vaginal cavity; or a tumor capsule, or any surgically created space (for example the space created by surgical removal of a tumor or abscess, surgical debridement of tissue and the like) or any space or area occupied by a tumor, abscess, diseased tissue, implant, prosthesis or any foreign body.

[0011] The term "body portion" includes any tissue of the body, for example but not limited to: breast tissue, cardiovascular tissue, central nervous system tissue, colon tissue, connective tissue, endometrial tissue, gastrointestinal tissue, heart tissue, heart valve tissue, liver tissue, muscle tissue, nasal cavity, pancreatic tissue, placental tissue, rectal tissue, renal tissue, skin tissue, urogenital tissue; and any fluid or secretion of the body, for example but not limited to: amniotic fluid, aqueous humor of the eye, blister fluid, blood, cerebrospinal fluid, lacrimal secretions, plasma, saliva, serum, synovial fluid, tear fluid, urine, vaginal secretions, vitreous humor of the eye, and wound fluid; and includes the total or entire body, for example for systemic administration to the whole body.

[0012] A therapeutic benefit of thymosin beta 4 may include at least partial prevention and/or treatment of side effects and/or adverse effects caused by the administration of another drug. In certain embodiments, thymosin beta 4 may be administered in conjunction with drugs that cause adverse effects, such as autoimmune inflammatory attack. For example, thymosin beta 4 may be administered with the drug

ipilmumab to prevent side effects such as autoimmune inflammatory attack. Thymosin beta 4 may be administered before, during or after the drug is administered.

[0013] Further therapeutic benefits of thymosin beta 4 may also include the promotion of healing or at least partial prevention and/or treatment of damage, injury and/or other adverse changes in a live human patient due to one or more of the following conditions, which are not intended to be limiting:

Wound Healing and Tissue Repair

[0014] Revitalize scar tissue
[0015] Ameliorate wound healing disorder
[0016] Healing and repair of damage due to:
- **[0017]** Atherosclerosis
- **[0018]** Arthritis
- **[0019]** Burns
- **[0020]** Cardiovascular disease (e.g., atherosclerosis, congestive heart failure, myocardial infarction)
- **[0021]** Chronic wounds
- **[0022]** Infection (viral, bacterial, fungal)
- **[0023]** Ischemia (brain, bone, heart)
- **[0024]** Musculoskeletal disorders
- **[0025]** Neurological and nerve diseases
- **[0026]** Neuromuscular-degenerative diseases
- **[0027]** Osteoporosis
- **[0028]** Quaternary ammonium salt exposure
- **[0029]** Radiation damage (UV)
- **[0030]** Skin grafts
- **[0031]** Skin lesions
- **[0032]** Toxic chemicals
- **[0033]** Trauma
  - **[0034]** recurrent
  - **[0035]** surgical
- **[0036]** Ulcers
  - **[0037]** diabetic
  - **[0038]** pressure
  - **[0039]** venous

[0040] Healing and repair in:
- **[0041]** Breast tissue
- **[0042]** Cardiovascular tissue
- **[0043]** Central nervous system tissue
- **[0044]** Connective tissue
  - **[0045]** bone
  - **[0046]** cartilage
  - **[0047]** joints
- **[0048]** Epithelium
- **[0049]** Eye
  - **[0050]** cornea
  - **[0051]** retina
- **[0052]** Gastrointestinal tissue
- **[0053]** Liver
- **[0054]** Mucosa
- **[0055]** Muscle
- **[0056]** Neural tissue
  - **[0057]** nerve
- **[0058]** Pancreatic islets
- **[0059]** Skin
  - **[0060]** dermis
  - **[0061]** epidermis
- **[0062]** Urogenital
  - **[0063]** endometrium
  - **[0064]** placenta
  - **[0065]** uterus

Dermal Conditions

[0066] Dermatitis
- **[0067]** contact dermatitis
- **[0068]** atopic dermatitis

[0069] Eczema
[0070] Epidermolysis bullosa (healing of sores, blisters, skin degradation)
[0071] Psoriasis
[0072] Allergic or inflammatory reactions due to:
- **[0073]** Insect bites
- **[0074]** Irritants
- **[0075]** Poison ivy/oak/sumac
- **[0076]** Sensitizing agents
- **[0077]** Toxins
- **[0078]** Venomous reptiles and amphibians

[0079] Treating symptoms:
- **[0080]** Blister
- **[0081]** Burn
- **[0082]** Induration
- **[0083]** Inflammation
- **[0084]** Itching
- **[0085]** Rash
- **[0086]** Redness Swelling

[0087] Improving skin conditions associated with skin aging:
- **[0088]** Appearance
- **[0089]** Changes in actin ratios and turnover
- **[0090]** Changes in collagen and other matrix proteins
- **[0091]** Darkening (age spots)
- **[0092]** Decreased capacity to repair DNA damage
- **[0093]** Degeneration
- **[0094]** Elasticity (loss of)
- **[0095]** Increase in skin cancers
- **[0096]** Increased risk of infection
- **[0097]** Thinning

Ophthalmic Conditions

[0098] Elevated intraocular pressure (glaucoma)
[0099] Dry eye syndrome (xerophthalemia) due to:
- **[0100]** Age
- **[0101]** Antibiotics
- **[0102]** Anti-diarrheals
- **[0103]** Antihistamines
- **[0104]** Corneal irregularities
- **[0105]** Diuretics
- **[0106]** Hormonal changes (menopause)
- **[0107]** Large eyes
- **[0108]** Meibomitis
- **[0109]** Neurotrophic keratitis
- **[0110]** Sjogren's syndrome
- **[0111]** Systemic lupus erythematosis
- **[0112]** Thyroid disease
- **[0113]** Uveitis

[0114] Trauma to the eye due to:
- **[0115]** Chemical injury
- **[0116]** Contact lens wear
- **[0117]** Diabetes (keratopathy, retinopathy)
- **[0118]** Infection/inflammation
  - **[0119]** blepharites
  - **[0120]** conjunctivitis
  - **[0121]** iritis
  - **[0122]** keratitis
  - **[0123]** meibomitis

[0124] Mooren's ulcers
[0125] optic neuritis
[0126] retinitis
[0127] scleritis
[0128] temporal arteritis
[0129] uveitis
[0130] Physical trauma
[0131] Quaternary ammonium salts (corneal thinning)
[0132] Recurrent corneal abrasion
[0133] Rheumatoid arthritis (corneal melts)
[0134] Surgery
[0135] cataract
[0136] epithelial debridement
[0137] corneal resurfacing
[0138] LASIK
[0139] PRK

Cardiovascular Conditions

[0140] Aging
[0141] Apoptotic death of neurovascular cells
[0142] C-reactive protein (cardiovascular disease risk)
[0143] Clotting and vessel occlusion
[0144] extracellular matrix build-up (body tissue or fluid transport vessel)
[0145] plaque (coronary vessels following stenting or angioplasty)
[0146] restenosis
[0147] stenosis
[0148] Congestive heart failure with or due to:
[0149] Pulmonary edema
[0150] Atherosclerosis
[0151] Diabetes
[0152] Obesity
[0153] Tobacco use
[0154] Alcohol abuse
[0155] Cocaine use
[0156] Developmental defect
[0157] Heart valve defects
[0158] Infarction
[0159] Infection
[0160] Ischemia
[0161] Myocardial infarction and damage occurring at time of myocardial event
[0162] Reperfusion injury (damage caused by increase in blood flow)
[0163] Stroke
[0164] Transformation of cardiac endothelium to mesenchyme (enhance or down-regulate)
[0165] Trauma
[0166] Other heart failure

General Conditions

[0167] Infectious and Inflammatory Diseases
[0168] Acne and acne vulgaris
[0169] Acute generalized exanthematous pustulosis
[0170] Allergic aspergillosis
[0171] Ankylosing spondylitis
[0172] Anthrax
[0173] Arthritis
[0174] crystal
[0175] infectious
[0176] juvenile chronic
[0177] osteo
[0178] psoriatic
[0179] reactive
[0180] rheumatoid
[0181] Asthma
[0182] Behcet's disease
[0183] Beret's disease
[0184] Bovine spongiform encephalopathy
[0185] Bronchiolitis
[0186] Bronchiolitis obliterans organizing pneumonia
[0187] Chronic bronchitis
[0188] Chronic obstructive pulmonary disease
[0189] Chirg-Strauss syndrome
[0190] Cholangitis
[0191] Colic
[0192] Colitis and ileitis
[0193] Cranial arteritis
[0194] Creutzfeld-Jakob disease
[0195] Crohn's disease
[0196] Cryptogenic pulmonary eosinophilia
[0197] Dermatitis
[0198] atopic
[0199] contact and allergic contact
[0200] seborrheic
[0201] stasis
[0202] Eczema
[0203] Emphysema
[0204] Epidermolysis bullosa
[0205] Erythema elevatum diutinum
[0206] Escherichia coli
[0207] Fibrosing alveolitis
[0208] Gall bladder infection
[0209] Gastrointestinal fistulae
[0210] Gingivitis
[0211] Graft rejection
[0212] Graft versus host disease
[0213] Helicobacter pylori
[0214] Hemolytic anemia
[0215] Hypersensitivity pneumonitis
[0216] Idiopathic thromocytopenic purpura
[0217] Inflammatory bowel disease
[0218] Job's syndrome
[0219] Leprosy
[0220] Lung inflammation
[0221] Lupoid hepatitis
[0222] Malaria
[0223] Methocillin-resistant Staphylococcus aureus (MRSA)
[0224] Netherton's syndrome
[0225] Obstructive airway diseases
[0226] Pancreatitis
[0227] Periodontal disease (aggressive, chronic, necrotizing)
[0228] Peritonitis
[0229] Pneumocysitis carinii pneumonia
[0230] Pneumonia
[0231] Polyarteritis nodosa
[0232] Polymyalgia rheumatica
[0233] Pouchitis
[0234] Psoriasis
[0235] Pustular lesions
[0236] Pyoderma gangrenosum
[0237] Regional enteritis
[0238] Sarcoidosis
[0239] Septic shock

[0240] Sinusitis
[0241] Sjogren's syndrome
[0242] Sweet's syndrome
[0243] Subcorneal pustular dermatosis
[0244] Systemic lupus erythematosis
[0245] Tissue reaction to implanted prostheses
[0246] Tuberculosis
[0247] Ulcerative colitis
[0248] Ulcers
[0249] Urticaria
[0250] Vancomycin-resistant Enterococcus (VRE)
[0251] Vasulitis
[0252] hypersensitivity
[0253] allergic cutaneous
[0254] Wegener's granulomatosis
[0255] Neuro-, Muscular- and Neuromuscular Diseases
[0256] Alcoholism
[0257] Alexander's disease
[0258] Alper's disease
[0259] Alzheimer's disease
[0260] Amyotrophic lateral sclerosis
[0261] Ataxia telangiectasia
[0262] Autism
[0263] Batten disease
[0264] Canavan disease
[0265] Cockayne syndrome
[0266] Corticobasal degeneration
[0267] Frontotemporal lobar degeneration
[0268] Huntington's disease
[0269] HIV-associated dementia
[0270] Kennedy's disease
[0271] Krabbe's disease
[0272] Lewy body dementia
[0273] Machado-Joseph disease
[0274] Multiple sclerosis
[0275] Muscular dystrophy (Duchenne, Becker)
[0276] Myasthenia gravis
[0277] Narcolepsy
[0278] Neuroborreliosis
[0279] Neurodegenerative and demyelinating diseases
[0280] Niemann Pick disease
[0281] Parkinson's disease
[0282] Pelizaeus-Merzbacher disease
[0283] Pick's disease
[0284] Primary lateral sclerosis
[0285] Prion diseases
[0286] transmissible spongiform encephalopathies
[0287] bovine spongiform encephalopathy
[0288] Creutzfeld-Jakob disease
[0289] Progressive supranuclear palsy
[0290] Refsum's disease
[0291] Sandhoff's disease
[0292] Schilder's disease
[0293] Subacute combined degeneration of spinal cord
[0294] Spinocerebellar ataxia
[0295] Spinal muscular atrophy
[0296] Steele-Richardson-Olszewski disease
[0297] Stroke
[0298] Tabes dorsalis
[0299] Traumatic brain injury
[0300] Cell Proliferative Disorders
[0301] Cancer
[0302] Diabetic retinopathy
[0303] Leukemia
[0304] Lymphoma
[0305] Multiple myeloma
[0306] Neovascular glaucoma
[0307] Psoriasis
[0308] Other Uses
[0309] Early pregnancy maintenance
[0310] Fibrotic tissue disorders
[0311] Osteoporosis
[0312] Protect tissue from UV radiation damage
[0313] Restore impaired T-lymphocyte blastogenic response
[0314] Sclerotic disorders
[0315] Wound healing disorders
[0316] Uses to Increase
[0317] axonal myelination
[0318] brain remodeling at locations of brain injury
[0319] cell migration
[0320] cellular proliferation in adult brain
[0321] collagen IV
[0322] differentiation of neural progenitor cells into mature glia
[0323] differentiation of neural progenitor cells into mature neurons
[0324] elastin
[0325] migration of neural progenitor cells
[0326] migration/differentiation of oligodendrocyte progenitor cells
[0327] myelination of damaged axons
[0328] neural progenitor cell proliferation
[0329] nerve regeneration and/or brain remodeling
[0330] neurite outgrowth
[0331] neuron survival
[0332] production of L1
[0333] Uses to Inhibit
[0334] angiogenesis (in cancer)
[0335] apoptosis in a tissue
[0336] ILBa phosphorylation
[0337] inflammation in a tissue
[0338] inflammatory responses
[0339] NF-kappaB-mediated activation and translocation
[0340] tissue cytotoxicity
[0341] UV radiation damage

[0342] A physician or health care provider may first determine a desired concentration of thymosin beta 4 (or a desired increase in concentration of thymosin beta 4 from an existing level) in a body portion of a live human patient in need of treatment. The physician or health care provider may then calculate the dosage necessary to achieve the desired concentration using the formula:

$$C=(A)D.t^{-B} \quad \text{(Formula I)},$$

or

$$D=C/(A)(t^{-B}) \quad \text{(Formula IA)},$$

wherein C is the predetermined thymosin beta 4 concentration to be provided in ng/mL, D is the dosage of thymosin beta 4 administered in mg, t is the time elapsed after administration of an initial dosage of thymosin beta 4 in hours (t is treated as a constant in this equation), A is about 30 to about 38, and B is about 0.5 to about 1. According to one embodiment, the formula is

$$C=(35.6)D.t^{-0.754} \quad \text{(Formula II)}.$$

Time, t, may be 1, and D may equal C/35.6.

[0343] The above formulas were developed by analysis of data from human patients who had been administered differ-

ent dosages of thymosin beta 4. The frequency of dosing needed between dosages to achieve the desired concentration over time, multiplied by the dosage, gave the total drug administered in a 24-hour period. The dosage that maintained the required concentration with the lowest total drug administered was termed the most efficient. See Exampe I, below.

[0344] Based on the data collected, concentrations of TB4 in the body portion follow (especially soon after administration, with a decreasing correlation over time) a power function. An estimation of the concentration of thymosin beta 4 at 1 hour was determined using this model with an average within 10% of the experimental mean for the concentrations tested. The concentrations in the tested patients at 1 hour give an approximate range that can be efficiently maintained because the concentrations at about 1 hour are approximately 15% of the initial concentration (mean 14.7%, median 13.3%). The concentration found in human patients at 5 minutes after initial administration intravenously was defined as the initial concentration, and as C_{max}, i.e. the maximum concentration achieved after administration of a dose. For the calculations made in the studies, the range of concentration which is the effective and desired dose was assumed to be 5-25% of this initial concentration (C_{max}). In general, intervals between intravenous treatment times of about an hour also are the most reliably efficient in achieving and maintaining a particular concentration. Therefore, in certain embodiments, when calculating dosage using Formula I or Formula II, t may equal about 1. The concentration which is achieved with a particular dosage of thymosin beta 4 at 5 minutes (C_{max}) can be found using Formula I by calculating C using the particular dosage (D) and 0.083 hours (5 minutes) as t.

[0345] Using Formula II, concentration at 1 hour is (35.6) D. In certain embodiments, the formula gives the concentration with an average error of about 10%, calculated against the experimental mean from in vivo patient data. Formulas I and II where t=1, therefore, provide a reasonable estimation of a concentration that is an acceptable and effective concentration to provide therapeutic treatment. The average concentration at a time of 1 hour after administration from the experimental data was 15.7%±1.32% (SD) of C_{max}. Therefore, without wishing to be bound by theory, assuming 5-25% of the initial (5-minute) concentration is an effective and efficient concentration range for a particular treatment, and that the concentration at a time of one hour is about 15% of the initial concentration (C_{max}), then the treatment concentration range would fall within (A)D±0.67(A)D, or from about 0.33 (A)D to about 1.67(A)D.

[0346] The actual desired concentration to be achieved in a body portion of a live human patient for treatment of a condition is determined by a physician and may depend on many factors known in the art, such as the indication (disease to be treated) for which the thymosin beta 4 is to be administered, the patient's size, gender, and age, other disease conditions present in the patient (e.g., autoimmune disease, diabetes, renal disease), the presence of neutralizing antibodies to TB4 in the patient, endogenous or pre-existing levels of TB4, and general metabolism. Generally these concentrations will range from about 1 ng/mL to about 10 mg/mL or about 200 pM to about 2 mM. In other embodiments, concentrations range from about 10 ng/mL to about 1 mg/mL, about 10 ng/mL to about 100 μg/mL, about 10 ng/mL to about 10 μg/mL, or about 100 ng/mL to about 1 μg/mL.

[0347] With respect to the levels for treatment of cardiac diseases, certain embodiments will be in about a 6 mg/kg to 18 mg/kg range for dosing (420 mg and 1260 mg unit dose, respectively), which correspond to Cmax levels of about 90,000-350,000 ng/mL.

[0348] The range of time over which the formulas are useful is about 5 minutes to about 3 hours (e.g., about 30 minutes to about 2 hours, for example, about 1 hour). According to certain embodiments, the formulas may be used with t=about 0.67 to about 1.5 hours, for example, about t=1. When calculating values using times of 1.5 hours or greater, the formulas may be those wherein A=about 30 and B=about 0.8 to about 1. According to certain embodiments, for times of 1.5 hours or greater and especially for times of 2 hours or greater, A may equal about 30 and B may equal about

[0349] Administration of thymosin β4 to a body portion can be achieved by injection (including intravenous injection, subcutaneous injection, intramuscular injection, intraperitoneal injection, direct local injection) into the body portion, infusion, osmotic pump and the like, or by other means such as topical application to a wound or to any external or internal body surface, transdermal administration, oral administration, rectal administration, vaginal administration, ocular administration, buccal administration, and the like. Formulations for use can take any convenient form, such as, for example, sterile injectable liquids, topical creams and ointments, transdermal patches, eye drops, oral rinses, irrigation solutions and other liquids, gels, or semi-solids for topical administration to a body surface or body compartment, or any acceptable pharmaceutical formulation or dosage form known in the art.

EXAMPLES

Example 1

Analysis of TB4 Concentration Data.

[0350] Treatment regimens to maintain a given dose (data summary):

Infusion dosage per dose	Frequency of administration	Total TB4 required for 24 hour treatment
Concentration >1000 ng/mL in blood		
*42 mg	2 hours	504 mg
140 mg	3 hours	1120 mg
420 mg	6 hours	1680 mg
1260 mg	9 hours	3360 mg
Concentration >5000 ng/mL in blood		
42 mg	10 minutes	6048 mg
*140 mg	1 hour	5040 mg
*420 mg	2 hours	5040 mg
1260 mg	4 hours	7560 mg
Concentration >10000 ng/mL in blood		
42 mg	5 minutes	12096 mg
*140 mg	20 minutes	10080 mg
*420 mg	1 hour	10080 mg
*1260 mg	3 hours	10080 mg
Concentration >20000 ng/mL in blood		
~42 mg	n/a	n/a
140 mg	10 minutes	20160 mg
*420 mg	40 minutes	15120 mg
*1260 mg	2 hours	15120 mg

-continued

Infusion dosage per dose	Frequency of administration	Total TB4 required for 24 hour treatment
Concentration >40000 ng/mL in blood		
~42 mg	n/a	n/a
~140 mg	n/a	n/a
420 mg	10 minutes	60480 mg
*1260 mg	1 hour	30240 mg

~indicates first dose does not bring TB4 concentration that high

*indicates the most efficient treatment (as determined by total required)

Example 2.

Thymosin Dosage Regimens.

[0351] A patient in need of thymosin beta 4 treatment with a concentration of 10,000 ng/mL exogenous thymosin beta 4 is administered thymosin beta 4 according to a dosage schedule wherein D and t are calculated using $C=(35.6)D*t^{0.754}$.

[0352] A patient in need of thymosin beta 4 treatment with a concentration of 10,000 ng/mL exogenous thymosin beta 4 with a 1-hour dosing frequency is administered $D=C/(A)t^{-B}$=10,000 ng/mL/(35.6)($1^{-0.75}$h)=281 mg thymosin beta 4.

Example 3

[0353] A patient in need of thymosin beta 4 treatment with a concentration of 10,000 ng/mL exogenous thymosin beta 4 using 200 mg unit dosage forms of thymosin beta 4 is administered one dosage form about every $t=(C/DA)^{(-1/B)}$=10,000 ng/mL/((35.6)(200 mg))$^{(-1/0.754)}$=0.637 hours.

[0354] Thymosin beta 4 is available in single-use vials containing, for example, 200 mg per vial, to maintain sterility. A patient in need of thymosin beta 4 treatment with a concentration of 10,000 ng/mL exogenous thymosin beta 4 is administered thymosin beta 4 according to a dosage schedule wherein t is calculated using $\log_B(AD/C)$, the equation can be used to determine at what time (t) to administer thymosin beta 4.

[0355] t=10,000 ng/mL/((35.6)(200 mg))$^{(-1/0.754)}$=0.637 hours (−38 minutes).

1. A method of, providing a desired concentration of administered thymosin beta 4 (TB4) in a body portion of a live human patient in need thereof, at a predetermined time t, which comprises:

(a) determining a thymosin beta 4 treatment dosage (D) using Formula I

$$C=(A)D*t^{-B} \quad \text{(Formula I)},$$

wherein C is the predetermined concentration at time t, in ng/mL, D is the dosage of thymosin beta 4 to be administered to said live human patient in mg, t is the time elapsed after administration of dosage D in hours, A is about 30 to about 38, and B is about 0.5 to about 1; and

(b) administering said dosage (D) of thymosin beta 4 to said live human patient so as to achieve said desired concentration of administered thymosin beta 4 in said body portion.

2. The method of claim **1** which comprises further administering said dosage (D) of thymosin beta 4 to said live human patient at intervals of time t.

3. The method of claim **1** wherein C is about 100 ng/mL to about 100,000 ng/mL thymosin beta 4.

4. The method of claim **1** wherein C is about 500 ng/mL to about 50,000 ng/mL thymosin beta 4.

5. The method of claim **1** wherein C is about 1000 ng/mL to about 40,000 ng/mL thymosin beta 4.

6. The method of claim **1** wherein C is about 5000 ng/mL to about 10,000 ng/mL thymosin beta 4.

7. The method of claim **1** wherein t is about 5 minutes to about 3 hours.

8. The method of claim **1** wherein t is about 30 minutes to about 2 hours.

9. The method of claim **1** wherein t is about 1 hour.

10. The method of claim **1** wherein A is about 31 to about 37.

11. The method of claim **1** wherein A is about 32 to about 36.

12. The method of claim **1** wherein A is about 33 to about 36.

13. The method of claim **1** wherein A is about 35.6.

14. The method of claim **1** wherein B is about 0.6 to about 0.9.

15. The method of claim **1** wherein B is about 0.7 to about 0.8.

16. The method of claim **1** wherein B is about 0.75.

17. The method of claim **1** wherein B is about 0.754.

18. The method of claim **1** wherein Formula I is:

$$C=(35.6)D*t^{-0.754}.$$

19. The method of claim **1** which comprises further administering said dosage (D) of thymosin beta 4 to said live human patient at intervals of time t.

20. The method of claim **18** which comprises further administering said dosage (D) of thymosin beta 4 to said live human patient at intervals of time t.

21. The method of claim **1** wherein said thymosin beta 4 is administered in conjunction with another drug, wherein said thymosin beta 4 is administered before, during or after said drug.

22. A method of providing a desired concentration of administered thymosin beta 4 (TB4) in a body portion of a live human patient in need thereof, at a predetermined time, t, which comprises:

(a) determining a time (t) for administering a thymosin beta 4 treatment dosage (D) using Formula I

$$C=(A)D*t^{-B} \quad \text{(Formula I)},$$

wherein C is the predetermined concentration at time t, in ng/mL, D is the dosage of thymosin beta 4 to be administered to said live human patient in mg, t is the time elapsed after administration of dosage D in hours, A is about 30 to about 38, and B is about 0.5 to about 1; and

(b) administering said dosage (D) of thymosin beta 4 to said live human patient so as to achieve said desired concentration of administered thymosin beta 4 in said body portion.

23. A method of maintaining TB4 concentration within an efficient TB4 concentration range in a body portion of a live human patient in need thereof, over time, comprising:

(a) selecting a target TB4 concentration, C, in said body portion,

(b) maintaining said TB4 concentration within said efficient TB4 concentration range by administering TB4 to said live human patient by calculating (1) the dosage amount to be administered, D, and (2) the time at which said dosage amount, D, is administered, t, according to Formula I:

$$C=(A)D*t^{-B} \quad \text{(Formula I)},$$

wherein C is a target TB4 concentration in ng/mL, wherein D is the treatment dosage to said live human patient in mg, wherein t is the time elapsed after an initial administration of TB4 to said live human patient in hours, wherein A is about 30 to about 28, and wherein B is about 0.5 to about 1;

(c) administering said treatment dosage, D, of TB4 to said live human patient at time, t, so as to achieve said target concentration of administered TB4; and

(d) repeating (b) and (c) to maintain the concentration of TB4 in said body portion within ±10% of said target concentration, C.

24. A method of treatment to provide a desired concentration range of TB4 in a body portion of a live human patient in need thereof, over a period of time while minimizing the total amount of TB4 which is administered over said period of time, t, which comprises:

(a) selecting a desired concentration, C, of TB4 to be achieved in said live human patient;

(b) calculating a TB4 dosage amount, D, to be administered to said live human patient using Formula I:

$$C=(A)D*t^{-B} \quad \text{(Formula I)},$$

wherein C is said desired concentration, C, in ng/mL, D is said treatment dosage to said live human patient in mg, t is about 1 hour, A is about 30 to about 38, and B is about 0.5 to about 1;

(c) calculating the total amount of TB4 that is to be administered daily in (b);

(d) calculating a TB4 dosage amount, D, to be administered to said live human patient using Formula I:

$$C=(A)D*t^{-B} \quad \text{(Formula I)},$$

wherein C is said desired concentration, C, in ng/mL, D is said treatment dosage to said live human patient in mg, t is other than about 1 hour, A is about 30 to about 38, and B is about 0.5 to about 1;

(e) calculating the total amount of TB4 that is to be administered daily in (d);

(f) determining whether the total amount of TB4 to be administered in (b) or in (d) is lower; and

(g) administering TB4 to said live human patient at the dosage amount, D, and time, t, which results in said lower total amount of administered TB4 to said live human patient.

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