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Pharmaceutical composition comprising an alpha-ketoalkanoic acid ester or -amine and lactic acid or a lactic acid salt

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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING AN ALPHA-KETOALKANOIC ACID ESTER OR -AMINE AND LACTIC ACID OR A LACTIC ACID SALT

(57) Abstract: Disclosed is a pharmaceutical composition comprising an ester of an alpha-ketoalkanoic acid or an amide of an alpha-ketoalkanoic and lactic acid or a pharmaceutically acceptable salt of lactic acid dissolved in aqueous solution.

PHARMACEUTICAL COMPOSITION COMPRISING AN ALPHA-KETOALKANOIC ACID ESTER OR
-AMIDE AND LACTIC ACID OR A LACTIC ACID SALT

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No.
5 60/373,680, filed on April 17, 2002, the entire teachings of which are incorporated
herein by reference.

GOVERNMENT SUPPORT

The invention was supported, in whole or in part, by grants from the Defense
10 Advanced Research Projects Agency (N65236-00-1-5434) and NIH grants
GM58484, GM37631 and GM68481. The Government has certain rights in the
invention.

BACKGROUND OF THE INVENTION

15 Esters of alpha-ketoalkanoic acids such as ethyl pyruvate have been
described for use in treating reperfusion injury (WO01/24793), inflammatory
disorders (WO02/074301) and renal failure (WO02/081020). The entire teachings of
these publications are incorporated by reference herein. Notwithstanding the
acceptance of esters of alpha-ketoalkanoic acids as effective therapeutic agents,
20 esters of alpha-ketoalkanoic acids are typically unstable in aqueous solutions,
presumably due to hydrolysis of the ester. For example, a sharp drop in pH from 6 to
about 2 can occur in as few as four hours when such esters are dissolved in aqueous
solutions. Such solutions are unsuitable for administration to patients unless used
immediately after mixing. The full potential of esters of alpha-ketoalkanoic acids as
25 therapeutic agents is unlikely to be realized without the development of
pharmaceutical formulations in which the ester is stable.

SUMMARY OF THE INVENTION

It has now been discovered esters of alpha-ketoalkanoic acids remain stable
30 in aqueous formulations comprising lactate. For example, a Lactated Ringers
Balanced Salt Solution comprising 1%, 5% and 10% by weight of ethyl pyruvate

showed a relatively reduced drop in pH over a 48 hour period (Example 1). Based on this discovery, novel pharmaceutical formulations comprising esters of alpha-ketoalkanoic acids and methods of using the same in therapy are disclosed herein.

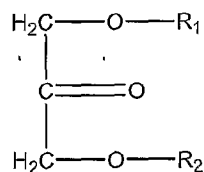
The disclosed invention is a pharmaceutical composition comprising an ester
5 or amide of an alpha-ketoalkanoic acid and lactic acid or a pharmaceutically acceptable salt of lactic acid (i.e., lactate).

The pharmaceutical compositions of the present invention offer several advantages including high stability of alpha-ketoalkanoic acid esters compared with previously known formulations of such compounds. They are suitable for use in
10 humans for at least 48 hours after mixing.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is a pharmacological composition comprising an aqueous solution of an ester of an alpha-ketoalkanoic acids or an amide of an alpha-
15 ketoalkanoic acid.

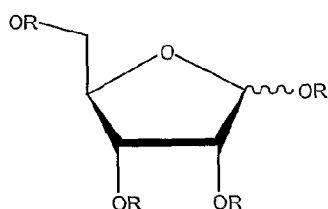
In one aspect, the ester of the alpha ketoalkanoic acid used in the disclosed formulation is, for example, an ester of a C₃-C₈ straight-chained or branched alpha-ketoalkanoic acid. Examples include an ester of alpha-keto-butanoic acid, alpha-ketopentanoic acid, alpha-keto-3-methyl-butanoic acid, alpha-keto-4-methyl-
20 pentanoic acid or alpha-keto-hexanoic acid. Pyruvic acid is preferred. A variety of groups are suitable for the ester position of the molecule, e.g., alkyl (preferably, C1-C3 alkyl), aralkyl, alkoxyalkyl or carbalkoxyalkyl. Specific examples include ethyl, propyl, butyl, carbmethoxymethyl (-CH₂COOCH₃), carbethoxymethyl (-CH₂COOCH₂CH₃), acetoxymethyl (-CH₂OC(O)CH₃), carbmethoxyethyl
25 (-CH₂CH₂COOCH₃), carbethoxyethyl (-CH₂CH₂COOCH₂CH₃), methoxymethyl (-CH₂OCH₃) and ethoxymethyl (-CH₂OCH₂CH₃). Ethyl esters are preferred. Thiolesters (e.g., wherein the thiol portion is cysteine or homocysteine), are also included. Other groups suitable for esterification of alpha-ketoalkanoic acids include dihydroxyacetone esters of formula



wherein R_1 is pyruvyl and R_2 is H, pyruvyl or a C1-C3 acyl, such as acetyl or propionyl;

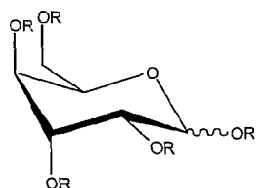
and monosaccharide esters such as, e.g., ribosyl esters

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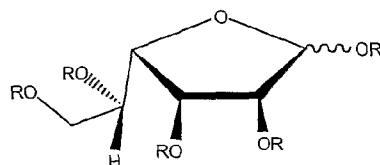


wherein each R is independently H, pyruvyl or a C1-C3 acyl, such as acetyl or propionyl, and at least one R is a pyruvyl,

10 or glucosyl esters



or



wherein each R is independently H, pyruvyl or a C1-C3 acyl, such as acetyl or propionyl, and at least one R is a pyruvyl.

15

In a preferred embodiment, the disclosed pharmaceutical composition comprises ethyl pyruvate, propyl pyruvate, butyl pyruvate, carbmethoxymethyl pyruvate, carbethoxymethyl pyruvate, acetoxymethyl pyruvate, carbmethoxyethyl pyruvate, carbethoxyethyl pyruvate, methoxymethyl pyruvate and ethoxymethyl pyruvate. Other preferred examples include ethyl alpha-keto-butyrate, ethyl alpha-keto-pentanoate, ethyl alpha-keto-3-methyl-butyrate, ethyl alpha-keto-4-methyl-pentanoate, or ethyl alpha-keto-hexanoate. Ethyl pyruvate is more preferred.

20

Suitable amides of alpha-ketoalkanoic acids for use in the disclosed formulations include compounds having the following structural formula:
RCOCONR₁R₂. R is an alkyl group; R₁ and R₂ are independently -H, alkyl, aralkyl, alkoxyalkyl, carboxyalkyl or -CHR₃COOH; and R₃ is the side chain of a naturally occurring amino acid. Preferably, the amide of an alpha-ketoalkanoic acids is a pyruvamide.

Suitable alkyl groups include C₁-C₈ straight chained or branched alkyl group, preferably C₁-C₆ straight chained alkyl groups.

Suitable aryl groups include carbocyclic (e.g., phenyl and naphthyl) and heterocyclic (e.g., furanyl and thiophenyl) aromatic groups, preferably phenyl.

An alkoxy group is -OR₄, wherein R₄ is an alkyl group, as defined above. An alkoxyalkyl group is an alkyl group substituted with -OR₄.

An aralkyl group is -XY, wherein X is an alkyl group and Y is an aryl group, both as defined above.

A carboxyalkyl group is an alkyl group substituted with -COOH. A carbalkoxyalkyl group is an alkyl group substituted with ester. Specific examples of ester substituents include ethyl, propyl, butyl, carbmethoxymethyl, carbethoxymethyl, acetoxymethyl, carbmethoxyethyl, carbethoxyethyl, methoxymethyl and ethoxymethyl. Ethyl esters are preferred.

The compositions of the present invention can comprise pharmaceutically acceptable salts of lactic acid at concentration from about 1 mM to about 100 mM. Example of pharmaceutically acceptable salts of lactic acid include, but are not limited to, lithium lactate, sodium lactate, potassium lactate, ammonium lactate, calcium lactate and magnesium lactate. In a preferred embodiment, sodium or potassium lactate are used.

The pharmaceutical compositions of the present invention can further include one or more of pharmaceutically acceptable salts of divalent cations such as Ca²⁺ or Mg²⁺ and monovalent cations such as Li⁺, Na⁺, K⁺, NH₄⁺ and the like. Sodium, potassium and calcium are preferable. Concentration of any one salt can vary from 0 to about 250 mM, preferably from about 10 mM to about 250 mM. Preferably, the salts are sodium chloride, potassium chloride, and calcium chloride. In a preferred

embodiment, the amount of any one salt or a combination of salts is sufficient to render the composition isotonic (having physiological osmolarity of blood plasma).

The ester of the alpha-ketoalkanoic acid (e.g. pyruvate) is preferably present in the pharmaceutical formulation at a concentration from about 0.1 to about 10% by weight, preferably 2% to about 5% by weight, more preferably 2.5%-3.5% by weight.

In a preferred embodiment, the pharmaceutical composition of the present invention comprises:

- (a) from about 0.1 % by weight to about 10% by weight of an ester of an alpha-ketoalkanoic acid (e.g., ethyl pyruvate); and
- (b) sodium or potassium lactate at a concentration from about 1 mM to about 100 mM.

In preferred embodiments, the compositions of the present invention further comprise:

- (c) from about 10 mM to about 250 mM of NaCl;
- (d) from about 0.1 mM to about 25 mM of KCl;
- (e) from about 0.1 mM to about 25 mM of CaCl₂.

In one preferred embodiment, the composition of the present invention comprises:

- (a) about 2% by weight to about 5% by weight of ethyl pyruvate;
- (b) about 50 to about 150 mM of NaCl;
- (c) about 1 to about 8 mM of KCl;
- (d) about 1 to about 5 mM of CaCl₂; and
- (e) about 10 to about 40 mM of sodium lactate,

wherein the ingredients (a) through (e) are dissolved in an aqueous solution. More preferably, the ester in part (a) described above is present at between about 2.5% to 3.5% by weight.

One preferred example of a composition of the present invention is a Ringer's Lactate solution, which contains potassium chloride (0 to about 4 mM), sodium chloride (about 100 to about 156 mM), calcium chloride (about 2.5 mM to about 3.0 mM), and sodium lactate (about 25 mM to about 30 mM) for example, as described herein.

The pharmaceutical formulation of the present invention can be used to treat and/or ameliorate disorders such as acute renal failure and ileus. As used herein, "ileus" is a partial or complete non-mechanical obstruction of the small and/or large intestine. Ileus occurs when peristalsis, the rhythmic contraction that moves material through the bowel, stops. Ileus can be caused, for example, by manipulation of the intestines during abdominal surgery, inflammation of the peritoneum, or administration of narcotics or chemotherapeutic agents.

The pharmaceutical compositions of the present invention can further be used for reanimation and resuscitation of mammals, e.g. humans, before, during and after mesenteric ischemia, mesenteric thrombus or mesenteric venous occlusion; aortic aneurism repair, coronary artery bypass, surgical treatment of arterial occlusion; hemorrhagic shock; and preservation or transplantation of organs. As used herein, "ischemia" is defined as interruption of oxygen supply, via blood flow, to an organ or to a part thereof.

The pharmaceutical compositions of the present invention can further be used to treat and/or alleviate cytokine-mediated inflammatory disorders. Such disorders include, but are not limited to, local and systemic inflammation, inflammatory bowel disease (Crohn's disease and ulcerative colitis), rheumatoid arthritis, asthma, sepsis, septic shock, inflammatory skin conditions such as psoriasis and eczema, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, endotoxic shock, Gram-negative shock, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption disease, reperfusion injury, graft v. host rejection, allograft rejection, fever and myalgia due to infection, cachexia secondary to infection or malignancy or secondary to AIDS, AIDS related complex, keloid and scar tissue formation.

The precise dose to be employed in a pharmaceutical composition of the present invention will depend on the route of administration, and the seriousness of the conditions, and should be decided according to the judgment of a practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The pharmaceutical compositions of the invention can be administered through a variety of routes, for example, oral, dietary, topical, intravenous, intramuscular, or by inhalation (e.g., intrabronchial, intranasal or oral inhalation, intranasal drops) routes of administration, depending on the agent and disease or condition to be treated, using routine methods in physiologically-acceptable inert carrier substances. Other suitable methods of administration can also include rechargeable or biodegradable devices, and slow release polymeric devices. For example, the therapeutic compositions can be administered in a sustained release formulation using a biodegradable biocompatible polymer, or by on-site delivery using micelles, gels, liposomes, or a buffer solution. Preferably, the pharmaceutical composition is administered as an infusate at a concentration of, e.g., 10 mM to 200 mM, preferably 20 mM to 90 mM of the active agent, at a rate of 1 mg/kg body weight/day to 200 mg/kg body weight/day, in a buffer solution as described herein. More preferably, the pharmaceutical composition is administered as an infusate at a concentration of about 28 mM of the active agent at a dose of 100 mg/kg body weight/day to 150 mg/kg body weight/day of alpha-ketoalkanoic acid, in a buffer solution. In bolus form, the active agent can be administered at a similar dosage, e.g., 1 mg/kg body weight/day to 200 mg/kg body weight/day of active agent, where the dosage is divided into aliquots and delivered 1 to 4 times daily (for a total dosage of 1 mg/kg body weight/day to 200 mg/kg body weight/day), with the concentration of the active agent adjusted accordingly.

EXEMPLIFICATION

Example 1 *Ethyl pyruvate is stable in Lactated Ringer's Solution over Forty-Eight Hours*

Formulations comprising ethyl pyruvate at various concentrations (5, 10, and 10 % by weight) were prepared by dissolving ethyl pyruvate in either commercially available Ringer's Lactate solution (potassium chloride (0 to about 4 mM), sodium chloride (about 100 to about 156 mM), calcium chloride (about 2.5 mM to about 3.0 mM), and sodium lactate (about 25 mM to about 30 mM)) or Ringer-like solution (potassium chloride (0 to about 4 mM), sodium chloride (about 100 to about 156

mM) and calcium chloride (about 2.5 mM to about 3.0 mM)), or IntralipidTM (1 000 mL contain: purified soybean oil 100-300 g, purified egg phospholipids 12 g, glycerol anhydrous 22 g, water for injection q.s. ad 1 000 mL. pH was adjusted with sodium hydroxide to pH approximately 8. Osmolality was about 300 mOsm/kg water). Acidity of each solution was measured at 0, 5, 30 and 60 minutes, 2, 4, 24, and 48 hours after dissolution of ethyl pyruvate. The results are presented in Table 1. As indicated by the pH readings, ethyl pyruvate remains stable in Ringer's Lactate solution, but not in Ringer-like solution or Intralipid.

Table 1

10

Stability of Ethyl Pyruvate in Three Different Formulation
as Measured by pH Change Over Time

	Ringer's lactate			Ringer's solution (no lactate)			Intralipid		
EP (%)	1	5	10	1	5	10	1	5	10
0 min	6.0	6.0	6.0	6.5	6.5	6.5	6.8	6.8	6.8
5 min	6.0	5.5	5.3	6.5	6.0	5.5	6.8	6.8	6.5
30 min	5.5	5.3	5.3	6.5	6.0	5.3	6.8	6.5	6.0
60 min	5.5	5.2	5.2	5.5	5.2	5.2	6.5	6.0	6.0
2 h	5.2	5.2	5.2	5.5	5.2	5.2	6.5	6.0	6.0
4 h	5.2	5.2	5.2	5.5	4.0	2.0	6.5	6.0	5.5
24 h	5.2	5.2	5.2	5.5	2.0	2.0	6.5	5.5	4.0
48 h	5.2	5.2	5.0	5.5	2.0	2.0	6.5	5.0	4.0

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

5 The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

10 Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A pharmaceutical composition comprising:
- 5 (a) an ester of an alpha-ketoalkanoic acid or an amide of an alpha-ketoalkanoic;
and
(b) lactic acid or a pharmaceutically acceptable salt of lactic acid dissolved in
aqueous solution.
2. A pharmaceutical composition comprising:
- 10 (a) an ester of an alpha-ketoalkanoic acid; and
(b) lactic acid or a pharmaceutically acceptable salt of lactic acid, dissolved in
aqueous solution.
3. The pharmaceutical composition of Claim 2, wherein said ester of an alpha-
15 ketoalkanoic acid is an ester of a C₃-C₈ straight-chained alpha-ketoalkanoic acid.
4. The pharmaceutical composition of Claim 3, wherein said ester of an alpha-
ketoalkanoic acid is an ester pyruvic acid.
- 20 5. The pharmaceutical composition of Claim 3, wherein said ester of an alpha-
ketoalkanoic acid is an ethyl ester.
6. The pharmaceutical composition of Claim 3, wherein said ester of an alpha-
ketoalkanoic acid is an alkyl, aralkyl, alkoxyalkyl or carbalkoxyalkyl ester.
- 25 7. The pharmaceutical composition of Claim 4, wherein said ester of pyruvic acid is
selected from the group consisting of ethyl pyruvate, propyl pyruvate,
carbmethoxymethyl pyruvate, acetoxymethyl pyruvate, carbethoxyethyl pyruvate,
and ethoxymethyl pyruvate.

8. The pharmaceutical composition of Claim 5, wherein said ester of an alpha-ketoalkanoic acid is selected from the group consisting of ethyl alpha-keto-butyrate, ethyl alpha-keto-pentanoate, and ethyl alpha-keto-hexanoate.
- 5 9. The pharmaceutical composition of Claim 3, wherein said alpha-ketoalkanoic acid ester is a glyceryl ester, a dihydroxyacetone ester, monosaccharide ester or a thiolester.
- 10 10. The pharmaceutical composition of Claim 6 wherein said ester of an alpha-ketoalkanoic acid is a C1-C3 alkyl ester.
11. The pharmaceutical composition of Claim 10, wherein the pharmaceutical composition comprises an ester of an alpha-ketoalkanoic acid and sodium or potassium lactate.
12. The pharmaceutical composition of Claim 11 further comprising a pharmaceutically acceptable salt of Na^+ , K^+ , NH_4^+ , Mg^{2+} , Ca^{2+} or a combination thereof.
- 15 13. The pharmaceutical composition of Claim 12 wherein the ester of an alpha-ketoalkanoic acid is ethyl pyruvate.
14. The pharmaceutical composition of Claim 12 wherein the pharmaceutically acceptable salts are NaCl, KCl, CaCl_2 or combinations thereof.
- 20 15. An aqueous pharmaceutical composition comprising:
 - (a) from 0.1% to 1.0% by weight of ethyl pyruvate; and
 - (b) sodium or potassium lactate at a concentration from about 1 mM to about 100 mM.
- 25 16. The pharmaceutical composition of Claim 15 further comprising:
 - (c) from about 10 mM to about 250 mM of NaCl;
 - (d) from about 0.1 mM to about 25 mM of KCl;

(e) from about 0.1 mM to about 25 mM of CaCl_2 .

17. A pharmaceutical composition comprising:

(a) about 2% to about 5% by weight of ethyl pyruvate;

(b) about 50 to about 150 mM of NaCl;

(f) about 1 to about 8 mM of KCl;

(g) about 1 to about 5 mM of CaCl_2 ; and

(h) about 10 to about 40 mM of sodium lactate,

wherein the ingredients (a) through (e) are dissolved in an aqueous solution.

18. A pharmaceutical composition comprising from about 0.1% to about 10% by weight of ethyl pyruvate in Ringer's Lactate solution.

19. The pharmaceutical composition of Claim 18 wherein the concentration of ethyl pyruvate is from about 2.5% to about 3.5% by weight.

20. A pharmaceutical composition of any one of Claims 1-19 substantially as herein before described with reference to the Figures and/or Examples.

20 DATED this 19th day of June, 2006

Critical Therapeutics, Inc.

By its Patent Attorneys

DAVIES COLLISON CAVE

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