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(54) Title: A SINGLE HIGH DOSE FLUOROQUINOLONE TREATMENT

(57) Abrégé/Abstract:
The present invention relates to treatment of animals with fluoroquinolones. More specifically, the present invention relates to the use of fluoroqunolones in a single high dose to replace multiple lower doses.

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A SINGLE HIGH DOSE FLUOROQUINOLONE TREATMENT

ABSTRACT OF THE DISCLOSURE

The present invention relates to treatment of animals with fluoroquinolones. More specifically, the present invention relates to the use of fluoroqunolones in a single high dose to replace multiple lower doses.

A SINGLE HIGH DOSE FLUOROQUINOLONE TREATMENT

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to treatment of animals with fluoroquinolones. More specifically, the present invention relates to the use of fluoroquinolones in a single high dose to replace multiple lower doses.

Brief Description of the Prior Art

Generally, the art teaches the use of fluoroquinolones in treating diseases such as bovine respiratory disease in feedlot cattle. Daily doses for three to five consecutive days have been used to treat bovine respiratory and other diseases. Heretofore, the art has not taught the use of a single elevated dose of a fluoroquinolone to treat the likes of bovine respiratory disease. Single treatment antimicrobials other than fluoroquinolones are effective based on specific formulations which prolong the release of active ingredient and extend the blood and tissue levels of animals treated therewith. Failure to use a single high dose might have been due to the perceived need for a special formulation to prolong the blood levels.

By the present invention, there is provided a single high dose treatment of fluoroquinolone to replace repeated treatments without the need for special prolonged release formulations.

DESCRIPTION OF THE INVENTION

In accordance with the foregoing, the present invention encompasses an improved process for treating subject animals by administering thereto a pharmaceutically effective amount of a fluoroquinolone, or a salt or ester thereof, the improvement comprising a high dose equivalent to the total dose normally administered daily for several days.

In another aspect of the invention, there is provided use of a fluoroquinolone, or a salt or ester thereof, in the manufacture of a medicament for treating animals, more especially for treating bovine respiratory disease, wherein said medicament is a single high dose medicament, and comprises the fluoroquinolone, or a salt or ester thereof, in a dose of from 5 mg/kg to 30 mg/kg.

In still another aspect of the invention, there is provided a pharmaceutical composition for treating an animal, more especially for treating bovine respiratory disease, in a single high dose, comprising a fluoroquinolone, or a salt or ester

thereof, in association with a pharmaceutically acceptable carrier, said single dose being from 5 mg/kg to 30 mg/kg.

In a further aspect of the invention, there is provided fluoroquinolone, or a salt or ester thereof, for use in treating animals, more especially for treating bovine respiratory disease, in a single high dose of said fluoroquinolone, or a salt or ester thereof, said single high dose being from 5 mg/kg to 30 mg/kg.

Non-limiting examples of fluoroquinolones can be selected from the group consisting of enrofloxacin, amifloxacin, benofloxacin, danofloxacin, difloxacin, flerofloxacin, fleroxacin, lomefloxacin, marbofloxacin, norfloxacin, ofloxacin, perfloxacin, rufloxacin, sarafloxacin and temafloxacin. The fluoroquinolone preferred herein is enrofloxacin.

Enrofloxacin is a fluoroquinolone carboxylic compound or a salt thereof. More specifically, enrofloxacin is 1-cyclopropyl-7-(4-ethyl-1-piperazinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid. Suitable salts are those of inorganic or organic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, acetic acid, succinic acid, phosphonic acid, malic acid, sodium hydroxide, potassium hydroxide, aluminum hydroxide, piperidine, morpholine, ethylamine, and triethylamine. The enrofloxacin and a method of preparing the same is described in U. S. Patent 4,670,444.

In accordance with the invention, the enrofloxacin can be formulated into a pharmaceutically effective composition that can be administered in a single high dose. The composition can be prepared by art-known techniques, for example, by mixing the active ingredient with a physiologically acceptable carrier. The carrier can be water and/or a member of the class selected from the group consisting of amino acids, metal hydroxides, alcohols, organic and inorganic acids and glycols. Specific examples thereof can be selected from the group consisting of arginine, potassium hydroxide, benzyl alcohol, citric acid, hydrochloric acid and propylene glycol. The resulting pharmaceutical composition is typically an injectable solution containing from 10 mg/mL to 350 mg/mL and preferably 20 mg/mL to 150 mg/mL and most preferably 100 mg/mL of the active ingredient comprising the enrofloxacin.

In treating animals in accordance with the invention, the pharmaceutical composition is administered to the subject animals in a high single dose of 5 mg/kg to 30 mg/kg and preferably 7.5 mg/kg to 12.5 mg/kg.

Surprisingly, it has been found that a single, high dose of fluoroquinolones can be administered to effectively treat disease such as bovine respiratory disease, e.g. *Pasteurella haemolytica* or *Pasteurella multocida* and swine pneumonia such as *Actinobacillius pleuro-pneumonia*.

The invention is further illustrated by the following non-limiting examples.

EXAMPLES

Example #1

In this example, a formulation of enrofloxacin was used to treat bovine respiratory disease. The formulation of enrofloxacin was administered to subject animals subcutaneously either as a repeated daily dose of 2.5 mg/kg or a single dose of 7.5 or 15.0 mg/kg. Response to treatment was determined by mortality (ability to prevent death), success (clinical cure), percent lung consolidation (percent of damaged lung remaining following treatment) and weight gain (healthy animals gain better than sick animals). The results are presented in the following table:

Number Animals	Dose	Number Mortality	Number Success	% Lung Consolidation	Weight Gain (kg)
12	0	4	0	37.9	2.3
12	2.5 x 3 days	0	7	13.9	7.7
12	7.5 x 1 day	0	7	15.9	6.7
12	15.0 x 1 day	0	8	14.4	5.8

The three treatment groups were not significantly different from each other in any of the variables examined.

Example #2

In this example a formulation of enrofloxacin was used to treat bovine respiratory disease. The formulation of enrofloxacin was given to subject animals either as a repeated daily dose of 2.5 mg/kg per day or as a single dose of 5.0 mg/kg or 7.5 mg/kg. These treatment groups were compared to a negative control (no treatment) and an established prolonged action single injection of macrolide or tilmacosin. The results are presented in the following table:

Number of Animals	Dose	Number Mortality	Number Success
14	0	3	2
27	5.0 x 1 day	0	8
28	7.5 x 1 day	0	14
28	2.5 x 3 days	0	13
28	Tilmicosin	1	13

The results demonstrate 7.5 mg/kg of enrofloxacin given as a single injection is as effective as 3 daily injections of 2.5 mg/kg enrofloxacin. It is also as effective as a single injection of the long acting tilmicosin.

Example #3:

In this example a formulation of enrofloxacin was used to treat pleuropneumonia in swine. The formulation of enrofloxacin was administered to the subject animals subcutaneously either as a repeated daily dose of 2.5 mg/kg or as a single dose of 2.5, 5.0, 7.5 or 10 mg/kg.

The results are presented in the following table:

Number Animals	Dose	Number Mortality	Number Success	% Lung Consolidation	Weight Gain (lbs)
12	0	2	1	22	5
12	2.5 x 1 day	0	6	2	15
12	5.0 x 1 day	0	9	12	19
12	7.5 x 1 day	0	10	5	18
12	10.0 x 1 day	0	9	7	20
12	2.5 x 3 days	0	8	4	18

The results clearly demonstrate that 7.5 and 10 mg/kg given as a single injection are as effective as 3 daily injections of 2.5 mg/kg enrofloxacin.

Although the invention has been described in detail in the foregoing for the purpose of illustration, it is to be understood that such detail is solely for that purpose and that variations can be made therein by those skilled in the art without departing from the spirit and scope of the invention except as it may be limited by the claims.

CLAIMS:

1. Use of a fluoroquinolone, or a salt or ester thereof, in the manufacture of a medicament for treating bovine respiratory disease, wherein said medicament is a single high dose medicament, and comprises the fluoroquinolone, or a salt or ester thereof, in a dose of from 5 mg/kg to 30 mg/kg.

2. The use of claim 1, wherein the fluoroquinolone is selected from the group consisting of amifloxacin, benofloxacin, danofloxacin, difloxacin, enrofloxacin, flerofloxacin, fleroxacin, lomefloxacin, marbofloxacin, norfloxacin, ofloxacin, perfloxacin, rufloxacin, sarafloxacin and temafloxacin.

3. The use of claim 2, wherein the fluoroquinolone is enrofloxacin.

4. The use of any one of claims 1 to 3, wherein the bovine respiratory disease is caused by *Pasteurella haemolytica* or *Pasteurella multocida*.

5. A pharmaceutical composition for treating bovine respiratory disease in a single high dose, comprising a fluoroquinolone, or a salt or ester thereof, in association with a pharmaceutically acceptable carrier, said single dose being from 5 mg/kg to 30 mg/kg.

6. The pharmaceutical composition of claim 5, wherein the fluoroquinolone is selected from the group consisting of amifloxacin, benofloxacin, danofloxacin, difloxacin, enrofloxacin, flerofloxacin, fleroxacin, lomefloxacin, marbofloxacin, norfloxacin, ofloxacin, perfloxacin, rufloxacin, sarafloxacin and temafloxacin.

7. The pharmaceutical composition of claim 6, wherein the fluoroquinolone is enrofloxacin.

8. The pharmaceutical composition of any one of claims 5 to 7, wherein the bovine respiratory disease is caused by *Pasteurella haemolytica* or *Pasteurella multocida*.

9. Fluoroquinolone, or a salt or ester thereof, for use in treating bovine respiratory disease, in a single high dose of said fluoroquinolone, or a salt or ester thereof, said single high dose being from 5 mg/kg to 30 mg/kg.

10. Fluoroquinolone, or a salt or ester thereof, of claim 9, wherein the fluoroquinolone is selected from the group consisting of amifloxacin, benofloxacin, danofloxacin, difloxacin, enrofloxacin, flerofloxacin, fleroxacin, lomefloxacin, marbofloxacin, norfloxacin, ofloxacin, perfloxacin, rufloxacin, sarafloxacin and temafloxacin.

11. Fluoroquinolone, or a salt or ester thereof, of claim 10, wherein the fluoroquinolone is enrofloxacin.

12. Fluoroquinolone, or a salt or ester thereof, of any one of claims 9 to 11, wherein the bovine respiratory disease is caused by *Pasteurella haemolytica* or *Pasteurella multocida*.