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(54) Domperidone at a low daily dose for use in the treatment or prevention of a disease associated with an alteration of the immune response

(57) The invention relates to the use of domperidone or a pharmaceutically acceptable salt thereof at low doses to prevent and/or treat a disease associated with an alteration of the immune response such as Leishmaniosis.

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Description

BACKGROUND OF INVENTION

Field of the Invention

[0001] The invention relates to the use of domperidone or a pharmaceutically acceptable salt thereof at low doses to prevent and/or treat a disease associated with an alteration of the immune response such as Leishmaniosis.

Description of the Related Art

[0002] Canine Leishmaniosis is a parasitical disease which is endemic in the countries of the Mediterranean basin where seroprevalence may reach a value of 48.4% (Alvar et al. 2004, Paradies et al 2006).

[0003] Leishmania parasites, similarly to what has also been described for other intracellular pathogenic agents, are able to survive and reproduce in the organism of several infected dogs thanks to their capacity to deviate the cellular type immune response (Th1) to the humoral type immune response (Th2). Actually, clinical evolution of the disease depends mainly of the immune response developed by the animal once it has been infected. Thus an infected animal will resist the progression of the disease while it manages to maintain a predominance of the cellular immune response (Th1), with a marked production of type Th1 cytokines, such as Interferon gamma o Interleukine IL-2, which are responsible for the macrophage's activation and, through it, for their leishmanicidal potential. Conversely, when humoral response (Th2) becomes predominant, which may occur immediately after infection or after a more or less prolonged period of resistance to disease progression, the animal succumbs to the disease and starts presenting clinical signs that may even lead to death (Chamizo et al. 2005, Brachelente et al. 2005).

[0004] In dogs, resistance to the disease appears to be associated to certain balance between Th1 and Th2 responses although cellular response (Th1) seems to predominate. In species such as the mouse, disease progression or animal resistance to the disease depends on a complete polarization of the immune response towards humoral (Th2) or celular (Th1), respectively. (Chamizo et al. 2005, Brachelente et al. 2005)

[0005] Therefore, the progression of the illness seems to be due to an alteration of the equilibrium between the cellular type immune response (Th1) and the humoral type immune response (Th2).

[0006] ES 2246142 describes the effect of Domperidone in the treatment of Leishmaniosis, administered at a dose of 2 mg/kg/day on dogs infected with L. Infantum, by means of the reestablishment of the equilibrium between the cellular type immune response (Th1) and the humoral type immune response (Th2) through an increase of prolactine blood levels. It shows that, at this dose, Domperidone is able to reduce the clinical signs of Leishmaniosis and/or to reduce the level of antibodies in infected animals.

[0007] As far as we know, there have been no attempts in the state of the art in treating or preventing Leshmaniosis in healthy or infected mammals using domperidone at a dose regime below 2 mg/kg/day. We are not aware either of any treatment or prevention method using Domperidone at a dose regime below 2 mg/kg/day during the latent phase of the illness or during secondary events or outbreaks of the illness.

[0008] In Merck 1997, it is described a recommended dose of Domperidone of 1mg/kg/day, however, this dose regimen is restricted to a different indication, namely as an antiemetic in dogs and not for the treatment of Leshmaniosis.

[0009] It would be of great interest to develop an improved use of Domperidone for the treatment of Leishmaniosis or a method of treatment of Leishmaniosis in which a lower dose regimen of Domperidone could be used in order to decrease the unnecessary toxicity of the active ingredient, but maintaining the same efficacy of the medicament as the one observed at higher dose regimens.

SUMMARY OF THE INVENTION

[0010] The present invention is based on the finding that domperidone or a pharmaceutically acceptable salt thereof may be used in a dosage regime or dose regimen, involving total daily amounts well below those so far suggested in the art to prevent and/or treat a disease associated with a decrease of the immune response. The use of lower dosage levels may allow minimization the occurrence of adverse effects.

[0011] Therefore, the present invention aims to find a method of treatment or prevention of Leshmaniosis in healthy or infected mammals using Domperidone with a dosage regime of 0.2-1 mg/kg/day having the same efficacy as the known dose regimes in the existing methods of treatment or prevention from the state of the art.

[0012] The present invention also aims to prepare formulations for the treatment or prevention of Leshmaniosis in healthy or infected mammals using Domperidone with a dose regime of 0.2-1 mg/kg/day providing the same efficacy as the known dose regimes in the existing methods of treatment or prevention from the state of the art.

[0013] The present invention is also directed to the use of Domperidone in combination with other drugs known to be useful for the treatment or prevention of Leshmaniosis in healthy or infected mammals (such as Leishmanicidal agents like N-methylglucamine antimoniate or Miltefosine, or such as Leishmaniostatic agents like Alopurinol) wherein the dosage regime provides the same efficacy as the known dose regimes in the existing methods of treatment or prevention from the state of the art.

DETAILED DESCRIPTION OF THE INVENTION

[0014] It is one aspect of the present invention the use of domperidone or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment or prevention in a mammal of a disease associated with a decrease of the immune response wherein the medicament is prepared for the administration of a daily dose of domperidone is from 0.2 mg/kg/day to 1 mg/kg/day. It is further preferred that the medicament is prepared for the administration of a daily dose of domperidone of from 0.3 mg/kg/day to 0.7 mg/kg/day, more preferably from 0.45 mg/kg/day 0.55 mg/kg/day and most preferably 0.5 mg/kg/day.

[0015] In one embodiment of the present invention the medicament is an oral dosage form intended for once a day administration. This embodiment facilitates adhesion of the patient to the therapeutic regime and thus compliance with this regime.

[0016] In an alternative embodiment of the present invention the medicament is an oral dosage form intended for twice a day administration.

[0017] In a preferred embodiment of the present invention the medicament is intended for use in the treatment of dogs.

[0018] In still another embodiment of the present invention domperidone is used in the form of its free base for the formulation of the medicament.

[0019] In an embodiment of the present invention the medicament is for the treatment or prevention in mammal of a disease associated to a decrease in cellular immunity mediated by CD4+Th1 lymphocytes. Examples of such diseases are:

- Leishmaniosis
- Parasitic diseases such as: malaria, other Trypanosomiasis, Ehrlichiosis, Toxoplasmosis and Coccidiosis,
- Immune diseases which progress with an increase in Th2 lymphocites and a decrease of Th1 such as asthma, atopies, hypersensitivity allergic reactions, and
- Viral diseases which progress with immunosuppression such as AIDS, herpesvirosis, adenovirosis, citomegalovirosis.

[0020] In a preferred embodiment of the present invention the medicament is for the treatment of leishmaniosis in mammal or to prevent its symptoms after infection has occurred.

[0021] In one embodiment of the present invention the medicament is prepared for the administration over a period of at least 10 days, preferably at least 15 days, more preferably at least 30 days.

[0022] The beneficial use of Domperidone in the treatment or prevention of Leshmaniosis in mammals (such as dogs) could be of high value when combined with a conventional treatment with a Leishmanicidal agent such as N-methylglucamine antimoniate or Miltefosine and/or a Leishmaniostatic agent such as Alopurinol.

[0023] In an embodiment of the invention Domperidone or a pharmaceutically acceptable salt thereof is used for the preparation of a medicament for the treatment or prevention in a mammal of a disease associated with an alteration of the immune response wherein the medicament is prepared for the combined administration of Alopurinol and a daily dose of domperidone of from 0.2 mg/kg/day to 1 mg/kg/day, preferably from 0.3 mg/kg/day to 0.7 mg/kg/day, more preferably from 0.45 mg/kg/day 0.55 mg/kg/day , most preferred 0.5 mg/kg/day.

[0024] In an embodiment of the invention Domperidone or a pharmaceutically acceptable salt thereof is used for the preparation of a medicament for the treatment or prevention in a mammal of a disease associated with an alteration of the immune response wherein the medicament is prepared for the combined administration of N-methylglucamine antimoniate and a daily dose of domperidone of from 0.2 mg/kg/day to 1 mg/kg/day, preferably from 0.3 mg/kg/day to 0.7 mg/kg/day, more preferably from 0.45 mg/kg/day 0.55 mg/kg/day , most preferred 0.5 mg/kg/day.

[0025] In an embodiment of the invention Domperidone or a pharmaceutically acceptable salt thereof is used for the preparation of a medicament for the treatment or prevention in a mammal of a disease associated with an alteration of the immune response wherein the medicament is prepared for the combined administration of Miltefosine and a daily dose of domperidone of from 0.2 mg/kg/day to 1 mg/kg/day, preferably from 0.3 mg/kg/day to 0.7 mg/kg/day, more preferably from 0.45 mg/kg/day 0.55 mg/kg/day , most preferred 0.5 mg/kg/day.

[0026] It is an embodiment of the invention the use of domperidone or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment or prevention in a mammal of a disease associated with an alteration of the immune response wherein the medicament is prepared for the combined administration of Alopurinol and N-methylglucamine antimoniate, and a daily dose of domperidone of from 0.2 mg/kg/day to 1 mg/kg/day, preferably from 0.3 mg/kg/day to 0.7 mg/kg/day, more preferably from 0.45 mg/kg/day 0.55 mg/kg/day , most preferred 0.5 mg/kg/day.

[0027] It is an embodiment of the invention the use of domperidone or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment or prevention in a mammal of a disease associated with an alteration of the immune response wherein the medicament is prepared for the combined administration of Alopurinol and Miltefosine, and a daily dose of domperidone of from 0.2 mg/kg/day to 1 mg/kg/day, preferably from 0.3 mg/kg/day to 0.7 mg/kg/day, more preferably from 0.45 mg/kg/day 0.55 mg/kg/day , most preferred 0.5 mg/kg/day.

[0028] Domperidone and the Leishmaniostatic agent

or the leshmanicidal agent can either be administered in a single dosage form or in separate dosage forms.

[0029] It is another aspect of the present invention a method for treating a mammal so as to increase the levels of prolactine in said mammal thereby preventing and/or treating a disease associated with a decrease of the immune response wherein said mammal is administered a daily dose of domperidone or a pharmaceutically acceptable salt thereof from 0.2 mg/kg/day to 1 mg/kg/day. It is further preferred to administer a daily dose of domperidone or a pharmaceutically acceptable salt thereof is from 0.3 mg/kg/day to 0.7 mg/kg/day, more preferably from 0.45 mg/kg/day 0.55 mg/kg/day and most preferably 0.5 mg/kg/day.

[0030] In one embodiment of the present invention the method is **characterized in that** domperidone or a pharmaceutically acceptable salt thereof is administered as an oral dosage form intended for once a day administration which facilitates adhesion of the patient to the therapeutic regime and thus compliance with this regime.

[0031] In an alternative embodiment of the present invention the method is **characterized in that** domperidone or a pharmaceutically acceptable salt thereof is administered as an oral dosage form intended for twice a day administration.

[0032] In a preferred embodiment of the present invention the method is used to treat dogs.

[0033] In still another embodiment of the present invention the method is **characterized in that** domperidone or a pharmaceutically acceptable salt thereof is used in the form of its free base for its incorporation in a medicament prior to administration to the mammal.

[0034] In an embodiment of the present invention the method of treatment is used to treat or prevent a disease associated to a decrease in cellular immunity mediated by CD4+Th1 lymphocytes. Examples of such diseases are:

- Leishmaniosis
- Parasitic diseases such as: malaria, other Trypanosomiasis, Ehrlichiosis, Toxoplasmosis and Coccidiosis,
- Immune diseases which progress with an increase in Th2 lymphocites and a decrease of Th1 such as asthma, atopies, hypersensitivity allergic reactions, and
- Viral diseases which progress with immunosuppression such as AIDS, herpesvirosis, adenovirosis, citomegalovirosis.

[0035] In a preferred embodiment of the present invention the method of treatment is used to treat leishmaniosis or to prevent its symptoms after infection has occurred.

[0036] In one embodiment of the present invention the treatment is maintained over a period of at least 10 days, preferably at least 15 days, more preferably at least 30 days.

[0037] In an embodiment of the invention, the beneficial use of Domperidone or a pharmaceutically acceptable salt thereof in the treatment or prevention of Leshmaniosis in mammals (such as dogs) could be of high value when carried out after a conventional treatment with a Leishmanicidal agent like N-methylglucamine antimoniate or Miltefosine and/or a Leishmaniostatic agent like Alopurinol once the parasite charge has been reduced in the infected animal, helping thereby the animal in recovering an effective immunologic response to the illness.

[0038] It is an embodiment of the invention a method for treating a mammal so as to increase the levels of prolactine in said mammal thereby preventing and/or treating a disease associated with a decrease of the immune response wherein said mammal is administered a combination comprising Alopurinol and a daily dose of domperidone or a pharmaceutically acceptable salt thereof from 0.2 mg/kg/day to 1 mg/kg/day. It is further preferred to administer a daily dose of domperidone is from 0.3 mg/kg/day to 0.7 mg/kg/day, more preferably from 0.45 mg/kg/day 0.55 mg/kg/day and most preferably 0.5 mg/kg/day.

[0039] It is an embodiment of the invention a method for treating a mammal so as to increase the levels of prolactine in said mammal thereby preventing and/or treating a disease associated with a decrease of the immune response wherein said mammal is administered a combination comprising N-methylglucamine antimoniate and a daily dose of domperidone or a pharmaceutically acceptable salt thereof from 0.2 mg/kg/day to 1 mg/kg/day. It is further preferred to administer a daily dose of domperidone is from 0.3 mg/kg/day to 0.7 mg/kg/day, more preferably from 0.45 mg/kg/day 0.55 mg/kg/day and most preferably 0.5 mg/kg/day.

[0040] It is an embodiment of the invention a method for treating a mammal so as to increase the levels of prolactine in said mammal thereby preventing and/or treating a disease associated with a decrease of the immune response wherein said mammal is administered a combination comprising Miltefosine and a daily dose of domperidone or a pharmaceutically acceptable salt thereof from 0.2 mg/kg/day to 1 mg/kg/day. It is further preferred to administer a daily dose of domperidone is from 0.3 mg/kg/day to 0.7 mg/kg/day, more preferably from 0.45 mg/kg/day 0.55 mg/kg/day and most preferably 0.5 mg/kg/day.

[0041] It is an embodiment of the invention a method for treating a mammal so as to increase the levels of prolactine in said mammal thereby preventing and/or treating a disease associated with a decrease of the immune response wherein said mammal is administered a combination comprising Alopurinol and N-methylglucamine antimoniate and a daily dose of domperidone or a pharmaceutically acceptable salt thereof from 0.2 mg/kg/day to 1 mg/kg/day. It is further preferred to administer a daily dose of domperidone is from 0.3 mg/kg/day to 0.7 mg/kg/day, more preferably from 0.45 mg/kg/day 0.55 mg/kg/day and most preferably 0.5

mg/kg/day.

[0042] It is an embodiment of the invention a method for treating a mammal so as to increase the levels of prolactine in said mammal thereby preventing and/or treating a disease associated with a decrease of the immune response wherein said mammal is administered a combination comprising Alopurinol and Miltefosine and a daily dose of domperidone or a pharmaceutically acceptable salt thereof from 0.2 mg/kg/day to 1 mg/kg/day. It is further preferred to administer a daily dose of domperidone is from 0.3 mg/kg/day to 0.7 mg/kg/day, more preferably from 0.45 mg/kg/day 0.55 mg/kg/day and most preferably 0.5 mg/kg/day.

[0043] Domperidone or a pharmaceutically acceptable salt thereof and the Leishmaniostatic agent or the leshmanicidal agent can either be administered in a single dosage form or in separate dosage forms.

[0044] The active compounds may be administered orally in the any suitable dosage form such as syrups, tablets, capsules, lozenges, controlled-release preparations, fast-dissolving preparations, lozenges, etc) or by injection (subcutaneous, intradermic, intramuscular, intravenous, etc.).

[0045] Formulations for injection administration include suspensions, solutions, emulsions in oily or aqueous vehicles, pastes, and implantable sustained-release or biodegradable formulations. Such formulations can further comprise one or more additional ingredients including suspending, stabilizing, or dispersing agents. In one embodiment of a formulation for parenteral administration, the active ingredient is provided in dry (i. e. powder or granular) form for reconstitution with a suitable vehicle (e. g. sterile pyrogen-free water) prior to parenteral administration of the reconstituted composition.

[0046] The pharmaceutical compositions can be prepared, packaged, or sold in the form of a sterile injectable aqueous or oily suspension or solution. This suspension or solution can be formulated according to the known art, and can comprise, in addition to the active ingredient, additional ingredients such as the dispersing agents, wetting agents, or suspending agents described herein. Such sterile injectable formulations can be prepared using a non-toxic parenterally- acceptable diluent or solvent.

[0047] Other parentally- administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form, in a liposomal preparation, or as a component of a biodegradable polymer systems. Compositions for sustained release or implantation can comprise pharmaceutically acceptable polymeric or hydrophobic materials such as an emulsion, an ion exchange resin, a sparingly soluble polymer, or a sparingly soluble salt.

[0048] The pharmaceutical formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient (s) association with the carrier. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[0049] Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil- in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

[0050] A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example natural, synthetic or semisynthetic oils or water with flavouring, sweetener and/or colouring agent.

Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used.

[0051] A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, lubricants, inert diluents, lubricating, surface active or dispersing agents. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered blend comprising the active compounds moistened with an inert liquid diluent and optionally dried and sieved. The tablets may optionally be coated or scored and may be formulated so as to provide modified (i. e. slow or controlled) release of the active ingredient therein.

[0052] Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatine capsule. Where the composition is in the form of a soft gelatine capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered.

DEFINITIONS AND CONVENTIONS

[0053] The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims.

[0054] Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

[0055] The term pharmaceutically acceptable salt embraces salts with a pharmaceutically acceptable acid or

base. Pharmaceutically acceptable acids include both inorganic acids, for example hydrochloric, sulfuric, phosphoric, diphosphoric, hydrobromic, hydroiodic and nitric acid and organic acids, for example citric, fumaric, maleic, malic, mandelic, ascorbic, oxalic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic, cyclohexylsulfamic (cyclamic) or p-toluenesulphonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases, for example alkyl amines, arylalkyl amines and heterocyclic amines.

[0056] In the context of infectious diseases the term prevention is not used to designate avoidance of infection of the patient with the infectious agent but the avoidance of the appearance of the clinical signs associated with disease progression after infection has occurred.

[0057] When quantities or doses of Domperidone or pharmaceutically stable salts thereof are mentioned in this application they refer to the quantities or doses expressed as Domperidone free base.

[0058] The term treatment is used to designate the control of disease progression once the clinical signs had appeared.

[0059] The present invention exhibits the advantages of reducing unnecessary toxicological effects of the drug when administered at higher doses to the mammal.

[0060] In case the dosage regime is administered once daily, this has the additional advantage of facilitating the compliance of the therapeutic dosage regimen (it is easier and more convenient to administer the medicament once daily).

[0061] A leshmanicidal agent is referred to an agent, which is able to kill the parasite which causes Leshmaniosis. A leshmaniostatic agent is referred to an agent, which does not kill the parasite which causes Leshmaniosis but instead is able to prevent its reproduction.

[0062] By "combined administration" , it has to be understood that Domperidone can be administered together or separately, simultaneously, concurrently or sequentially with a Leishmanicidal agent like N-methylglucamine antimoniate or Miltefosine and/or a Leishmaniostatic agent like Alopurinol in any order, e.g the administration of Domperidone can be made first, followed by the administration of the Leishmanicidal agent and / or the Leishmaniostatic agent, or the administration of Domperidone can be made last, preceded by the administration of the Leishmaniostatic agent and / or the the Leishmanicidal agent; or the administration of Domperidone can be made concomitantly with the Leishmaniostatic agent and / or the Leishmanicidal agent.

EXAMPLES

[0063] The advantages of the invention are more fully illustrated with reference to the following examples.

Example 1

[0064] Kinetic profile study of the prolactine hormone after domperidone oral administration in Beagle male dog

[0065] The present study was performed with the objective of determining the kinetic profile of the prolactine hormone in male dog after oral administration of domperidone at different dosage levels. 10 animals where used, which received a single oral administration of domperidone at six different dosage levels (0.125 mg/kg, 0.250 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg and 4 mg/kg) as well as a placebo, following a crossover trial in 7 phases separated by a minimal washing out period of 6 days. During each of the 7 phases blood samples were extracted at different times (t = 0h, 0.5h, 1h, 2h, 4h, 6h, 8h, 10h, 12h, 18h, 36 y 48h) for determining serum concentrations of prolactine using a commercial immunoenzymatic assay kit.

[0066] Although all the dosages produced a fast increase in the average concentrations of prolactine in blood, this increase was lower in the two lower dosage levels (0.125 and 0.250 mg/kg). With higher dosage levels (0.5 mg/kg, 1 mg/kg, 2 mg/kg and 4 mg/kg) increase was more pronounced but similar between them, not being possible to observe dose-effect correlation. In all cases the average concentrations of prolactine in the first 36 hours after domperidone administration remained above the prolactine concentration in the group treated with the placebo.

[0067] The greater values for the area under the curve of prolactine calculated between 0h and 12h (AUC) were obtained after the administration of domperidone at levels of 0.5 mg/kg and above. However, the values obtained after the administration at 1 mg/kg, 2 mg/kg and 4 mg/kg were not significantly greater than those obtained with the 0.5 mg/kg dosage.

[0068] In addition, the greater values of maximum concentration of prolactine (Cmax) were also obtained after the administration of domperidone at levels of 0.5 mg/kg dosage and above. Once again, the values obtained after its administration at 1 mg/kg, 2 mg/kg and 4 mg/kg were not significantly greater than those obtained with the 0.5 mg/kg dosage.

[0069] Finally, the time required to reach maximum prolactine concentration (Tmax) when domperidone was administered at levels of 0.5 mg/kg and above was lower than the time required after its administration at lower dosages (0.125 mg/kg and 0.250 mg/kg). In this case no statistically significant differences were observed between the 6 dosages studied.

[0070] The results surprisingly show that it is possible to administer dosage levels of domperidone to dogs below those described in the art (1 mg/kg/administration) while inducing the production of prolactine at levels comparable with those produced at the higher dosage described in the art. This effect is confirmed at dosages as small as 0.5 mg/kg.

Example 2

[0071] Study of the effect of domperidone administration on the cellular immune response in healthy dogs

[0072] The present study was undertaken to prove the effect of domperidone administration on the cellular immune response in healthy dogs through a controlled trial. 20 dogs of different breed, sex and age, were randomly distributed into two groups of 10. Animals from one of two groups worked as a negative control and did not receive any treatment. Animals from the other group received 0.5 mg domperidone/kg/day, orally, during 30 consecutive days. During the study several visits were paid (days 0, 15, 30, 60 and 90) during which some clinical examinations were done and blood samples were collected for biochemical, haemathological and serological analyses (DAT). The percentages of monocytes and neutrophils were determined in whole blood samples through the nitroblue tetrazolium (NBT) reduction test.

[0073] The results showed that in the group that did not receive any treatment the percentage of activated monocytes and neutrophils remained low and stable during the 90 monitored days. However, animals treated with domperidone suffered a statistically significant increase during the treatment, remaining high during at least 30 days after finishing the treatment.

[0074] The results surprisingly showed that domperidone administration at a dosage of 0.5 mg/kg/day on healthy dogs during 30 consecutive days, produced a stimulating effect of the cellular immune response that persists at least a month after finishing the treatment.

Example 3

[0075] Study of the response of the circulating monocyte-derived macrophages from healthy dog treated with domperidone, to the *in vitro* infection with *Leishmania infantum*

[0076] The objective of this study is to assess the effect of domperidone on the susceptibility to infection and the *in vitro* leishmanicidal capacity of circulating monocyte-derived macrophages exposed to *Leishmania infantum* promastigotes.

[0077] It is designed as a prospective monocentric study. A total of 10 dogs have been included, each of them acting as its own control, for which reason it has not been considered necessary the use of a negative control. All the animals received domperidone orally at a dosage of 0.5 mg/kg/day during 30 consecutive days. During the study several visits are paid the days 0 (basal), 15 and 30 of treatment, and days 60 and 90 (one and two months after finishing the treatment, respectively). During each visit blood is collected from animals and it is processed to isolate and culture monocytes-macrophages, which are then co-cultivated with *Leishmania* promastigotes. After 48 hours the nitroblue tetrazolium (NBT) reduction test is carried out on the cultures and the percentage of parasited macrophages and the number of amastigotes per macrophage. Blood samples are also collected on days 0 and 90 to assess animal health by biochemical and haemathological analyses.

[0078] These results have showed a significant increase of the phagocytic activity in the macrophages in the samples collected on days 15 and 30, even though the percentages of activated macrophages returned to their normal basic values in the samples collected on days 60 and 90. In parallel, and in concordance with the present results, the average percentage of infected macrophages, which in the cell culture from samples collected on day 0 was around 90%, decreased significantly down to around 25 % in samples collected on days 15 and 30, returning thereby to values close to the basic ones in samples collected on days 60 and 90. Finally, the number of amastigotes per infected macrophage followed a dynamic similar to the one described for the other two parameters.

[0079] According to the obtained results, it can be concluded that the daily administration of 0.5 mg/kg of Domperidone in dogs prepares the main cells involved in unspecific immunity (monocytes/macrophages) to an effective activation against infection by Leishmania, in experimental in-vitro conditions.

Example 4

[0080] Study of the clinical efficacy of a treatment plan with domperidone against canine leishmaniosis in its incipient stages

[0081] The objective of this study is the evaluation of the efficacy of an oral treatment plan with domperidone against canine leishmaniosis in its incipient stages, assessing its effect on the clinical illness incidence in a population of healthy animals resident in a highly endemic area.

[0082] It is designed as a field controlled clinical trial (treated group vs non-treated group) with 100 initially healthy animals (non-infected) resident in a highly endemic area, therefore with high possibilities to be infected. Half of the animals have received domperidone at a dosage of 0.5 mg/kg/day in accordance with a treatment plan that consists of repeatedly administering domperidone during periods of 30 days each four months ensuring that the treatment covers the onset and the end of the activity period of the transmitter insect to guarantee a double objective: In the first place reinforcing primary cellular response of the dog, so that when the insect infects the animal its primary defense barrier is prepared to beat the parasites resistance, to destroy them and to develop a specific immune response appropriate for the illness control/elimination. In the second place balancing the immune response of the animals which, having been infected during the periods of lower protection, are still in the initial phase of the illness.

[0083] Results of this study after one year from its inception, show that no animal having received treatment has shown symptoms of the illness, whereas approxi-

mately 30% of the animals which have not been treated have had to be withdrawn from the study because they showed clinical signs that indicated the development of the illness. Final results of this study are not yet available.

Claims

1. Use of domperidone or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment or prevention in a mammal of a disease associated with an alteration of the immune response wherein the medicament is prepared for the administration of a daily dose of domperidone of from 0.2 mg/kg/day to 1 mg/kg/day.

2. Use according to claim 1 **characterized in that** the medicament is prepared for the administration of a daily dose of from 0.3 mg/kg/day to 0.7 mg/kg/day.

3. Use according to claim 2 **characterized in that** the medicament is prepared for the administration of a daily dose of from 0.45 mg/kg/day 0.55 mg/kg/day.

4. Use according to claim 3 **characterized in that** the medicament is prepared for the administration of a daily dose of 0.50 mg/kg/day.

5. Use according to any preceding claim wherein the medicament is prepared as an oral dosage form for once a day administration.

6. Use according to any preceding claim **characterized in that** the mammal is a dog

7. Use according to any preceding claim **characterized in that** domperidone is used in the form of the free base.

8. Use according to any preceding claim **characterized in that** the disease is selected from the group of diseases associated to an alteration in cellular immunity mediated by CD4+Th1 lymphocytes.

9. Use according to claim 8 **characterized in that** the disease is leishmaniosis.

10. Use according to claim 8 **characterized in that** the disease is selected from the group comprising:

    - Parasitic diseases such as: malaria, other Trypanosomiasis, Ehrlichiosis, Toxoplasmosis and Coccidiosis,
    - Immune diseases which progress with an increase in Th2 lymphocites and a decrease of Th1 such as asthma, atopies, hypersensitivity allergic reactions, and
    - Viral diseases which progress with immunosuppression such as AIDS, herpesvirosis, adenovirosis, citomegalovirosis.

11. Use according to any preceding claim **characterized in that** the medicament is prepared for the administration over a period of at least 10 days.

12. Use according to claim 11 **characterized in that** the medicament is prepared for the administration over a period of at least 15 days.

13. Use according to claim 12 **characterized in that** the medicament is prepared for the administration over a period of at least 30 days.

14. Use according to any preceding claim wherein the medicament is prepared for the combined administration of domperidone and a Leishmanicidal agent such as N-methylglucamine antimoniate or Miltefosine.

15. Use according to claim 14 wherein the medicament comprises both domperidone and a Leishmanicidal agent such as N-methylglucamine antimoniate or Miltefosine either in a single dosage form or in separate dosage forms.

16. Use according to any preceding claim wherein the medicament is prepared for the combined administration of domperidone and a Leishmaniostatic agent such as Alopurionol.

17. Use according to claim 16 wherein the medicament comprises both domperidone and a Leishmaniostatic agent such as Alopurinol either in a single dosage form or in separate dosage forms.

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EUROPEAN SEARCH REPORT

Application Number
EP 09 38 2040

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