TITLE

A COMBINATION COMPOSITION COMPRISING IBUPROFEN AND PARACETAMOL

FIELD OF INVENTION

This invention relates to a combination composition comprising paracetamol and ibuprofen. A particularly preferred embodiment of the invention relates to a combination composition comprising these as active ingredients for use in relieving pain and/or inflammation.

BACKGROUND

Combinations of paracetamol and ibuprofen are known, for example as relatively low dose tablets having 150 mg ibuprofen and 500 mg. However there is a need for a medication, particularly one which can be administered intravenously in a hospital environment, which delivers higher doses of ibuprofen to provide pain relief in cases of severe or extreme pain. It is an object of one embodiment of the present invention to go at least some way towards facilitating this.

DEFINITIONS

References in this specification to an **adult** mean a person weighing 50 kg or more.

References in this specification to a **child** mean a person weighing less than 50 kg.

The term "**comprising**" and derivatives thereof, eg "comprises", if and when used herein in relation to a combination of features should not be taken as excluding the possibility that the combination may have further unspecified features.

SUMMARY OF INVENTION

According to one aspect of the invention there is provided a composition for providing relief for pain and/or inflammation, the composition having ibuprofen and paracetamol in combination for delivering to a human at each dose:

a) approximately 375 mg to approximately 425 mg ibuprofen,

b) approximately 575 mg to approximately 625 mg ibuprofen,

c) approximately 175 mg to approximately 225 mg ibuprofen, or

d) approximately 275 mg to approximately 325 mg ibuprofen,

in the case of option a) or b) in combination with approximately 975 mg to approximately 1,025 mg paracetamol, or in the case of options c) or d) in combination with approximately 475 mg to approximately 525 mg paracetamol.

Optionally the composition is for delivering to the human (preferably an adult) at each dose approximately 400 mg ibuprofen and approximately 1,000 mg paracetamol.

Optionally the composition is for delivering to the human (preferably an adult) at each dose approximately 600 mg ibuprofen and approximately 1,000 mg paracetamol.

Optionally the composition is for delivering to a child at each dose approximately 200 mg ibuprofen and approximately 500 mg paracetamol.

Optionally the composition is for delivering to a child at each dose approximately 300 mg ibuprofen and approximately 500 mg paracetamol.

Optionally the composition is for delivering the ibuprofen and paracetamol to the human (eg a child or adult) intravenously.

Optionally the composition is in the form of a solution.

Optionally the composition is in the form of a suspension.

A further aspect of the invention involves the use of ibuprofen and paracetamol in the manufacture of a medicament for treating pain and/or inflammation in a human, the medicament having:

a) approximately 375 mg to approximately 425 mg ibuprofen,

b) approximately 575 mg to approximately 625 mg ibuprofen,

c) approximately 175 mg to approximately 225 mg ibuprofen, or

d) approximately 275 mg to approximately 325 mg ibuprofen,

in the case of option a) or b) in combination with approximately 975 mg to approximately 1,025 mg paracetamol, or in the case of options c) or d) in combination with approximately 475 mg to approximately 525 mg paracetamol.

Optionally the medicament has approximately 400 mg ibuprofen and approximately 1,000 mg paracetamol. In this instance the medicament may be for treating an adult.

Optionally the medicament has approximately 600 mg ibuprofen and approximately 1,000 mg paracetamol. In this instance the medicament may be for treating an adult.

Optionally the medicament is for treating a child and has approximately 200 mg ibuprofen and approximately 500 mg paracetamol.

Optionally the medicament is for treating a child and has approximately 300 mg ibuprofen and approximately 500 mg paracetamol.

Optionally the medicament is for intravenous administration.

Optionally the composition is in the form of a solution.

Optionally the composition is in the form of a suspension.

According to a further aspect of the invention there is provided a method of treating a human to relieve pain and/or inflammation, comprising administering to the human:

a) approximately 375 mg to approximately 425 mg ibuprofen,

b) approximately 575 mg to approximately 625 mg ibuprofen,

c) approximately 175 mg to approximately 225 mg ibuprofen, or

d) approximately 275 mg to approximately 325 mg ibuprofen,

in the case of option a) or b) in combination with approximately 975 mg to approximately 1,025 mg paracetamol, or in the case of options c) or d) in combination with approximately 475 mg to approximately 525 mg paracetamol.

Optionally approximately 400 mg ibuprofen and approximately 1,000 mg paracetamol are administered to the human per dose. In this instance the human is preferably an adult.

Optionally approximately 600 mg ibuprofen and approximately 1,000 mg paracetamol are administered to the human per dose. In this instance the human is preferably an adult.

Optionally approximately 200 mg ibuprofen and approximately 500 mg paracetamol are administered to a child per dose.

Optionally approximately 300 mg ibuprofen and approximately 500 mg paracetamol are administered to a child per dose.

Optionally the composition is administered to the human (eg an adult or child) intravenously.

Optionally the composition is in the form of a solution.

Optionally the composition is in the form of a suspension.

DETAILED DESCRIPTION

In a preferred embodiment of the invention an intravenous solution is provided for use in treating severe pain in human patients. The solution is a combination medication comprising ibuprofen, paracetamol, purified water and suitable excipients as will be known to those with ordinary skills in the art of formulating intravenous medicines.

The excipients may be standard and may include one or more of suspending agents, viscosity regulating agents, buffering agents, wetting agents, preservatives, sweetening agents, flavouring agents and solvents.

The following examples illustrate preferred embodiments of the invention in the form of intravenous infusion solutions although the invention should not be seen as limited to these.

Ingredient	**Example 1** **mg/ 100ml vial**	**Example 2** **mg/ 100ml vial**	**Example 3** **mg/ 50ml vial**	**Example 4** **mg/ 50ml vial**
Ibuprofen	400	600	200	300
Paracetamol	1,000	1,000	500	500

For each of the above examples the two active ingredients are mixed with suitable amounts of the following excipients to give the vial volumes indicated in the above table:

- Cysteine hydrochloride monohydrate
- Disodium phosphate dehydrate
- Mannitol
- Hydrochloric acid
- Sodium hydroxide
- Purified water

Further examples of intravenous infusion solutions are provided below

Ingredient	**Example 5** **(adult dose)**	**Example 6** **(child dose)**
Ibuprofen arginine (active ingredient)	737 mg (corresponds to 400 mg ibuprofen)	368 mg (corresponds to 200 mg ibuprofen)
Paracetamol (active ingredient)	1,000 mg	500 mg
Reduced glutathione (antioxidant)	20 mg	20 mg
Sodium hydroxide or hydrochloric acid (pH modulator)	Sufficient to give a pH of 5-6	Sufficient to give a pH of 5-6

Sodium citrate (buffering agent)	10 mg	10 mg
Sodium chloride (isotonicity agent)	Sufficient to impart isotonicity	Sufficient to impart isotonicity
Purified water	Sufficient to bring the composition to 100 ml	Sufficient to bring the composition to 100 ml

All of the above infusion solutions are for delivery to a patient as a full dose, for example in each case the patient receives the complete vial contents as a 15 minute infusion every 6 hours. Examples 1, 2 and 5 are each an adult dose and Examples 3, 4 and 6 are each a child dose. In the case of very young or small children only part of the vial contents of Examples 3, 4 and 6 may be dosed, commensurate with instructions from the prescribing physician.

Paracetamol at 4,000 mg per 24 hour period, taken in 4 doses of 1,000 mg every 6 hours, has long been considered sufficient for relieving low level pain but for many patients suffering significant pain, for example in some post-operative situations, it is not sufficient. However it is generally not advisable to dose paracetamol at more than 1,000 mg per dose or at more than 4,000 mg per 24 hour period, because to do so can lead to undesirable side effects.

It is known to treat severe pain with ibuprofen in doses of 800 mg every 8 hours. However, doses as high as 800 mg can lead to undesirable side effects, for example adverse cardio renal conditions, thrombotic risks and gastrointestinal bleeding. Reducing the amount of ibuprofen at each dosing event may reduce the risk of side affects but at the same time may provide substantially less pain relief.

Surprisingly, a combination medicine comprising 600 mg or 400 mg ibuprofen, plus 1,000 mg paracetamol, for use every 6 hours, provides adequate pain relief for some patients that would otherwise take 800 mg ibuprofen every 8 hours. The lower dose of ibuprofen, ie 600 mg or 400 mg, versus 800 mg, may reduce the risk of undesirable side affects but the effectiveness of the medication is for such patients not compromised due to the presence of the paracetamol. This is unexpected

because one would not predict the presence of paracetamol at only 1,000 mg per dose to assist to any significant degree. The combination is counterintuitive because 800 mg ibuprofen for relief of severe pain is generally seen as an 8 hourly medicament, and 1,000 mg paracetamol is generally seen as a 6 hourly medicament for treating lower level pain. The normal dosage regimens for these active ingredients are out of step with one another, ie 8 hourly versus 6 hourly, and thus to the normally skilled artesian they would not, at the doses of the present invention, be seen as suitable for a combination medication.

Similar considerations apply in the case of 200 mg or 300 mg ibuprofen, in combination with 500 mg paracetamol, for treating children suffering from severe pain. In this regard, surprisingly, some children that would normally be given 400 mg ibuprofen for severe pain can be given, as an alternative, 200 mg or 300 mg ibuprofen, in combination with 500 mg paracetamol.

ALTERNATIVE CHEMICAL FORMS

While ibuprofen and paracetamol are specifically referred to in this specification, suitable other pharmaceutically acceptable forms of these two actives (eg salts, etc) may also be used and are intended to be embraced in the claims by references to the actives per se, with the weight amounts adjusted accordingly. For example, when a salt form is used, sufficient quantity may be included to meet the desired amount of the compound per se (eg, 200 mg ibuprofen corresponds with 368 mg ibuprofen arginine, or 342 mg ibuprofen lysinate). Thus, for example, a reference to 200 mg ibuprofen may be construed as sufficient to embrace the therapeutically equivalent amount of ibuprofen arginine or ibuprofen lysinate.

While some preferred forms of the invention have been described by way of example it should be appreciated that modifications and improvements can occur without departing from the scope of the appended claims.

CLAIMS

1. A combination composition for providing relief for pain and/or inflammation, the composition having ibuprofen and paracetamol and being suitable for use in delivering to a human intravenously at each dose:
    a) approximately 375 mg to approximately 425 mg ibuprofen, in combination with approximately 975 mg to approximately 1,025 mg paracetamol; or
    b) approximately 175 mg to approximately 225 mg ibuprofen, in combination with approximately 475 mg to approximately 525 mg paracetamol.

2. A composition according to claim 1, for delivering to the human at each dose approximately 400 mg ibuprofen and approximately 1,000 mg paracetamol.

3. A composition according to claim 2, wherein the human is an adult.

4. A composition according to claim 1, for delivering to a child at each dose approximately 200 mg ibuprofen and approximately 500 mg paracetamol.

5. A composition according to any one of claims 1 to 4, in the form of a solution.

6. A composition according to any one of claims 1 to 4, in the form of a solid suitable for mixing with a fluid to provide a solution.

7. A composition according to claim 1, for intravenous administration on a 12.5 mg paracetamol per kg body weight basis.

8. A composition according to claim 7, for administration every 6 hours.

9. The use of ibuprofen and paracetamol in the manufacture of a combination medicament for treating pain and/or inflammation in a human by intravenous administration, the medicament having:

a) approximately 375 mg to approximately 425 mg ibuprofen, in combination with approximately 975 mg to approximately 1,025 mg paracetamol; or

b) approximately 175 mg to approximately 225 mg ibuprofen, in combination with 475 mg to 525 mg paracetamol.

10. A use according to claim 9, wherein the medicament has approximately 400 mg ibuprofen and approximately 1,000 mg paracetamol.

11. A use according to claim 10, wherein the medicament is for treating an adult.

12. A use according to claim 9, wherein the medicament is for treating a child and has approximately 200 mg ibuprofen and approximately 500 mg paracetamol.

13. A use according to any one of claims 9 to 12, wherein the composition is in the form of a solution.

14. A use according to any one of claims 9 to 12, wherein the composition is in the form of a solid suitable for mixing with a fluid to provide a solution.

15. A use according to claim 9, wherein the composition is for intravenous administration on a 12.5 mg paracetamol per kg body weight basis.

16. A use according to claim 15, wherein the composition is for administration every 6 hours.