TITLE

A Combination Composition

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 containing these 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 paracetamol. However there is a need for a medication, particularly one which can be administered intravenously in a hospital environment. It is an object of an 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.

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, 513 mg ibuprofen lysinate, or 553 mg ibuprofen arginine salt, corresponds with 300 mg ibuprofen). Thus, for example, a reference to 300 mg ibuprofen may be construed as sufficient to embrace the therapeutically equivalent amount of ibuprofen lysinate or ibuprofen arginine.

The term "**comprising**" and derivatives thereof, eg "comprises", if and when used in relation to a combination of features should not be taken to exclude the possibility of the combination having further unspecified features.

SUMMARY OF INVENTION

According to one aspect of the invention there is provided an intravenous 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 125mg to approximately 175mg ibuprofen in combination with approximately 475mg to approximately 525 mg paracetamol; or

b) approximately 275mg to approximately 325mg ibuprofen in combination with approximately 975mg to approximately 1,025 mg paracetamol.

Preferably the composition is for dosing on approximately a 6 hourly basis.

Preferably the composition comprises:

a) approximately 150mg ibuprofen in combination with approximately 500mg paracetamol; or

b) approximately 300mg ibuprofen in combination with approximately 1,000 mg paracetamol.

Preferably the composition is in the form of a solution.

A further aspect of the invention comprises the use of paracetamol and ibuprofen in the manufacture of an intravenous medicament for treating pain and/or inflammation in a human wherein the medicament comprises, on a per dose basis:

a) approximately 125mg to approximately 175mg ibuprofen in combination with approximately 475mg to approximately 525 mg paracetamol; or

b) approximately 275mg to approximately 325mg ibuprofen in combination with approximately 975mg to approximately 1,025 mg paracetamol.

Preferably the composition is for dosing on approximately a 6 hourly basis

Preferably the composition comprises:

a) approximately 150mg ibuprofen in combination with approximately 500mg paracetamol; or

b) approximately 300mg ibuprofen in combination with approximately 1,000 mg paracetamol.

Preferably the composition is in the form of a solution.

A further aspect of the invention comprises a method of treating pain and/or inflammation by administering to a human, intravenously, a medicament comprising:

a) approximately 125mg to approximately 175mg ibuprofen in combination with approximately 475mg to approximately 525 mg paracetamol; or

b) approximately 275mg to approximately 325mg ibuprofen in combination with approximately 975mg to approximately 1,025 mg paracetamol.

Preferably the composition is administered on a 6 hourly basis.

Preferably the composition comprises:

a) approximately 150mg ibuprofen in combination with approximately 500mg paracetamol; or

b) approximately 300mg ibuprofen in combination with approximately 1,000 mg paracetamol.

Preferably the composition is in the form of a solution.

DETAILED DESCRIPTION

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

The following examples illustrate preferred embodiments of the invention in the form of intravenous infusion solutions.

Ingredient	**Example 1** **mg/ 100ml vial**	**Example 2** **mg/ 100ml vial**
Ibuprofen	150	300
Paracetamol	500	1,000

For each of the above examples the two active ingredients are mixed with suitable standard excipients to give the vial volumes indicated above.

The 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. Example 1 is a child's dose and Example 2 is an adult dose. In the case of very young or small children only part of the vial contents of Example 1 may be dosed on a body weight basis, 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, renal problems, thrombotic risks and gastrointestinal bleeding. Reducing the amount of ibuprofen at each dosing event may reduce the risk of side effects but at the same time may provide substantially less pain relief.

Surprisingly, an intravenous medicine comprising 150 mg or 300 mg ibuprofen, plus 500 mg or 1,000 mg paracetamol, respectively, for use every 6 hours, provides adequate pain relief for some patients that would otherwise need to take, respectively, 400mg or 800 mg every 8 hours. The lower dose of ibuprofen reduces the risk of undesirable side effects in some patients but the effectiveness of the medication for such patients is not compromised due to the presence of the

paracetamol. This is unexpected because for many patients one would not predict the presence of paracetamol to assist to any significant degree. The combination is counterintuitive because, for example, 400 mg ibuprofen for relief of pain is generally seen as an 8 hourly medicament, and 1,000 mg paracetamol is generally seen as a 6 hourly medicament. 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 150 mg ibuprofen, in combination with 500 mg paracetamol, for treating children suffering from pain. In this regard, surprisingly, some children that would normally be given 200 mg ibuprofen for pain can be given, as an alternative, 150 mg ibuprofen in combination with 500 mg paracetamol.

Administering an intravenous combination solution comprising 300 mg ibuprofen plus 1,000 mg paracetamol to an adult, or an intravenous combination solution comprising 150 mg ibuprofen plus 500 mg paracetamol to a child, on an ongoing basis, for example every 6 hours, provides a surprising level of pain relief compared to administering the same doses orally, for example by way of a tablet. The intravenous administration reduces the need for rescue pain relief in at least some patients recovering from surgical procedures. The intravenous administration may for example be by way of injection or infusion.

Example 3

In a particular embodiment of the invention an intravenous solution may be prepared by mixing the following active ingredients and excipients:

ACTIVE INGREDIENTS	**AMOUNT**
Paracetamol	1000 mg
Ibuprofen arginine	553 mg
EXCIPIENTS	**AMOUNT**
Reduced glutathione (as antioxidant)	20 mg
Sodium hydroxide or hydrochloric acid (as a pH modulator)	sufficient to give a pH of 5-6
Sodium citrate (as a buffering agent)	10 mg

Sodium chloride (as an isotonicity agent)	sufficient to impart isotonicity
Purified water	Sufficient to bring the composition to 100 ml

The solution is for administration to an adult as a single intravenous dose and further equivalent doses may be repeated every 6 hours if need be, commensurate with instructions from the prescribing physician.

Example 4

In a further embodiment of the invention an intravenous solution may be prepared by mixing the following active ingredients and excipients:

ACTIVE INGREDIENTS	**AMOUNT**
Paracetamol	500 mg
Ibuprofen arginine	276.5 mg
EXCIPIENTS	**AMOUNT**
Reduced glutathione (as antioxidant)	10 mg
Sodium hydroxide or hydrochloric acid (as a pH modulator)	sufficient to give a pH of 5-6
Sodium citrate (as a buffering agent)	5 mg
Sodium chloride (as an isotonicity agent)	sufficient to impart isotonicity
Purified water	Sufficient to bring the composition to 100 ml

The solution is for administration to a child as a single intravenous dose and further equivalent doses may be repeated every 6 hours if need be, commensurate with instructions from the prescribing physician.

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 following claims.

CLAIMS

1. An intravenous 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 125mg to approximately 175mg ibuprofen in combination with approximately 475mg to approximately 525 mg paracetamol; or

b) approximately 275mg to approximately 325mg ibuprofen in combination with approximately 975mg to approximately 1,025 mg paracetamol.

2. A composition according to claim 1, for dosing on approximately a 6 hourly basis.

3. A composition according to claim 1 or 2, comprising:

a) approximately 150mg ibuprofen in combination with approximately 500mg paracetamol; or

b) approximately 300mg ibuprofen in combination with approximately 1,000 mg paracetamol.

4. A composition according to claim 1, 2 or 3, in the form of a solution.

5. The use of paracetamol and ibuprofen in the manufacture of an intravenous medicament for treating pain and/or inflammation in a human wherein the medicament comprises, on a per dose basis:

a) approximately 125mg to approximately 175mg ibuprofen in combination with approximately 475mg to approximately 525 mg paracetamol; or

b) approximately 275mg to approximately 325mg ibuprofen in combination with approximately 975mg to approximately 1,025 mg paracetamol.

6. A use according to claim 5, wherein the composition is for dosing on approximately a 6 hourly basis

7. A use according to claim 5 or 6, whereion the composition comprises:

a) approximately 150mg ibuprofen in combination with approximately 500mg paracetamol; or

b) approximately 300mg ibuprofen in combination with approximately 1,000 mg paracetamol.

8. A use according to claim 5, 6 or 7, wherein the composition is in the form of a solution.

9. A method of treating pain and/or inflammation by administering to a human, intravenously, a medicament comprising:

a) approximately 125mg to approximately 175mg ibuprofen in combination with approximately 475mg to approximately 525 mg paracetamol; or

b) approximately 275mg to approximately 325mg ibuprofen in combination with approximately 975mg to approximately 1,025 mg paracetamol.

10. A method according to claim 9, wherein the composition is administered on a 6 hourly basis.

11. A method according to claim 9 or 10, wherein the composition comprises:

a) approximately 150mg ibuprofen in combination with approximately 500mg paracetamol; or

b) approximately 300mg ibuprofen in combination with approximately 1,000 mg paracetamol.