studies described herein, this was believed to owe, in part, to VSDL possessing a significantly longer circulatory $t_{½}$ of ~120 minutes and biological $t_{½}$ of ~>6 hours. In comparison, it has been reported that BNP has a circulating $t_{½}$ of ~3.1 minutes and biological $t_{½}$ of ~<½ hour [4, 6-9, 12 and 13]. In patients with volume overload, including those with CHF, circulating natriuretic peptides are elevated. This is thought to be indicative of a compensatory mechanism attempting to reinstate homeostasis. However, in severe congestion, it appears that the body is unable to produce sufficient quantities to restore balance.

The present applicant has now recognised that the benefits demonstrated in preclinical and clinical use of VDSL in the treatment of CHF are superior to those seen with the current natriuretic treatments for ADCHF[14], and hereby proposes VSDL administration to patients with chronic CHF or ADCHF as a safe and effective treatment for mediating beneficial haemodynamic effects with additional beneficial natriuretic, diuretic and renal effects, whilst regulating plasma volume and blood pressure (BP) within clinically acceptable ranges and without seriously adverse side effects. It is also anticipated that such VSDL treatment may reduce hospitalisation time and readmission rates for chronic CHF and ADCHF patients. Further, the present applicant has found that effective treatment of chronic CHF and ADCHF patients with VSDL can be achieved with doses that are substantially lower than expected.

SUMMARY OF THE INVENTION

~~In its broadest aspect,~~ The present invention provides a method of treating chronic congestive heart failure (CHF) or acute decompensated congestive heart failure (ADCHF) in a subject, said method comprising administering to the subject an effective amount of vessel dilator (VSDL) ~~a peptide derived from atrial natriuretic peptide (ANP) prohormone~~ or a mimetic thereof.

~~Preferably,~~ The method may be ~~is~~ used for treating chronic CHF with a symptom severity level of NYHA class III or~~, more preferably,~~ ADCHF ~~with a symptom severity level of NYHA class III or IV (ie where the subject shows "severe limitations [and] experiences symptoms even while at rest")~~.

The method may be suitable for the treatment of non-human primates and other mammals such as livestock (including race horses), exotic animals (eg tigers and elephants) and companion animals (eg dogs and cats), however typically the subject will be a human, in which case, the method is most preferably used for treating ADCHF characterised by:

1. Dyspnoea at rest or dyspnoea with minimal activity (ie difficulty breathing at rest while sitting, or difficulty breathing while lying flat or with one pillow, or difficulty breathing with minimal activity such as talking, eating); and
2. At least one of the following signs:
   - Tachypnoea with respiratory rate > 20 breaths per minute, or
   - Pulmonary congestion/oedema with rales or crackles/crepitations at least a third above lung bases; and

3. At least one of the following objective measures:

- Pulmonary oedema/congestions as shown by chest X-ray, or
- Circulating B-type natriuretic peptide (BNP) concentration of ≥400 pg/ml or circulating NT-proBNP concentration of ≥1000 pg/ml, or
- A PCWP > 20 mmHg or
- A systolic dysfunction within the last 12 months (EF < 50%) as determined by Trans-Thoracic Echocardiogram (TTE), nuclear testing, cardiac magnetic resonance imaging (MRI) or ventricular angiography).

The term "effective amount" as used herein refers to an amount of the VSDL peptide or mimetic that will elicit a desired biological or therapeutic response in the subject (eg beneficial haemodynamic effects with, preferably, additional beneficial natriuretic, diuretic and renal effects whilst regulating plasma volume and blood pressure (BP) within clinically acceptable ranges). The effective amount will, however, typically be in the range of 0.1 to 75 μg/kg/day. The effective amount of the VSDL peptide or mimetic is administered by infusion (preferably, by intravenous (*iv*) or subcutaneous (*sc*) infusion) as a single dose per day or, otherwise, across multiple times per day (eg 2 to 4 times per day). The effective amount of the VSDL peptide or mimetic may, for example, be administered by infusion at a rate of < 100 ng/kg/min, and preferably, at a rate of about ≤75 ng/kg/min, more preferably at a rate of about ≤50 ng/kg/min or ≤30 ng/kg/min, still more preferably at a rate of about ≤25 ng/kg/min, even still more preferably ≤ 20 ng/kg/min and, and yet still more preferably, at a rate of about ≤15 ng/kg/min.

In a further aspect, the present invention provides the use of VSDL ~~a peptide derived from atrial natriuretic peptide (ANP) prohormone~~ or a mimetic thereof in the manufacture of a medicament for infusion of the peptide or mimetic, for treating chronic congestive heart failure (CHF) or acute decompensated congestive heart failure (ADCHF) in a subject.

In a still further aspect, the present invention provides an infusion device containing, or provided with, a medicament comprising VSDL ~~a peptide derived from atrial natriuretic peptide (ANP) prohormone~~ or a mimetic thereof adapted for infusion of the peptide or mimetic, for treating chronic congestive heart failure (CHF) or acute decompensated congestive heart failure (ADCHF) in a subject.

BRIEF DESCRIPTION OF THE ACCOMPANYING FIGURES

Figure 1 provides tabulated response data for three ADCHF patients infused intravenously (*iv)* with 12.5 ng/kg/min for 60 minutes recorded from commencement of infusion (0 minutes) to 5 days post-infusion as indicated;

Figure 2 provides graphical representations of the results of Figure 1: (A) Mean arterial pressure (MAP),

(B) Pulmonary capillary wedge pressure (PCWP), (C) Cardiac index (CI), (D) Systemic vascular resistance (SVR), and NT-proBNP circulatory levels (ng/L); and

Figure 3 provides a graphical representation of measured VSDL concentrations in blood samples taken at the various time points, as corrected for a baseline (ie endogenous) VSDL concentration of 0.024 ng/ml.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the use of a peptide derived from atrial natriuretic peptide (ANP) prohormone (~~eg~~ ie VSDL) or a mimetic thereof, in a method for the treatment of chronic CHF or ADCHF in a subject comprising administering to a subject an effective amount of the peptide or mimetic (typically in the range of 0.1 to 75 μg/kg/day).

In a first embodiment, the present invention provides a method of treating chronic congestive heart failure (CHF) or acute decompensated congestive heart failure (ADCHF) in a subject, said method comprising administering to the subject an effective amount of VSDL ~~a peptide derived from atrial natriuretic peptide (ANP) prohormone~~ or a mimetic thereof in the range of about 0.1 to 5 μg/kg/day ~~by infusion at a rate of 1 to 400 ng per kg subject body weight per minute (ng/kg/min)~~.

In this embodiment, the effective amount of the VSDL peptide or mimetic ~~will preferably be in the range of 0.1 to 75 μg/kg/day, but more preferably in the range of about 0.1 to 25 μg/kg/day, still more preferably in the range of about 0.1 to 20 μg/kg/day or about 0.1 to 5 μg/kg/day, and even still more~~ is preferably, in the range of about 0.1 to 3.5 μg/kg/day or 0.1 to 1.5 μg/kg/day. Most preferably, the effective amount that is administered to the subject will be about 0.75 μg/kg/day.

The effective amount of the VSDL peptide or mimetic may, for example, be administered by infusion at a rate of < 100 ng/kg/min, and preferably, at a rate of about ≤75 ng/kg/min, more preferably at a rate of about ≤50 ng/kg/min or ≤30 ng/kg/min, still more preferably at a rate of about ≤25 ng/kg/min, even still more preferably ≤20 ng/kg/min and, and yet still more preferably, at a rate of about ≤15 ng/kg/min. Most preferably, the effective amount is infused at a rate in the range of 1 to 15 ng/kg/min and, in one particularly preferred form of the method of the first embodiment, the effective amount of the peptide or mimetic is administered to the subject by infusion at a rate of about 12.5 ng/kg/min.

The effective amount of the VSDL peptide or mimetic may be infused (preferably, by intravenous (*iv*) or subcutaneous (*sc*) infusion) as a single dose per day or, otherwise, across multiple times per day (eg as three equal separate doses at 0 hours, 6 hours and 12 hours).

Typically, a single dose (or each dose of a multidose regimen), will be infused over a period of about 60 minutes.

Where the rate of the infusion is at a preferred rate of ≤75 ng/kg/min, it is considered that a single dose over a period of about 60 minutes will provide an effective daily dose (ie of ≤4.5 μg/kg/day). Further, where lower infusion rates are employed of 25 ng/kg/min and 12.5 ng/kg/min, it is considered that a single dose over a period of 60 minutes will provide an effective daily dose of ≤1.5 μg/kg/day and ≤0.75 μg/kg/day, respectively.

~~Thus,~~ In a second embodiment, the present invention provides a method of treating ~~chronic congestive heart failure (CHF) or~~ acute decompensated congestive heart failure (ADCHF) in a subject, said method comprising administering to the subject an effective amount of VSDL ~~a peptide derived from atrial natriuretic peptide (ANP) prohormone~~ or a mimetic thereof. ~~, wherein said effective amount is ≤ 4.5 μg/kg/day.~~

In this embodiment, the effective amount of the VSDL ~~peptide~~ or mimetic will preferably be in the range of 0.1 to ~~3.5~~ 75 μg/kg/day, but more preferably in the range of about 0.1 to ~~1.5~~ 20 μg/kg/day. Most preferably, the effective amount that is administered to the subject will be about ~~0.75~~ 0.1 to 1.5 μg/kg/day.

In this embodiment, the VSDL is preferably administered by infusion at a rate of ≤75 ng/kg/min, but more preferably at a rate of ≤50 ng/kg/min. Typically, a single daily dose (or each dose of a multidose regimen), will be infused over a period of about 60 minutes).

~~Preferably,~~ The method of the first embodiment of the present invention ~~is~~ may be used for treating chronic CHF with a symptom severity level of NYHA class III ~~or, more preferably, ADCHF with a symptom severity level of NYHA class III or IV~~. The method of the first and second embodiments of the present invention may be used for treating ADCHF with a symptom severity level of NYHA class III or IV. Most preferably, the method is used for treating ADCHF in a human characterised by:

1. Dyspnoea at rest or dyspnoea with minimal activity (ie difficulty breathing at rest while sitting, or difficulty breathing while lying flat or with one pillow, or difficulty breathing with minimal activity such as talking, eating); and
2. At least one of the following signs:
   - Tachypnoea with respiratory rate > 20 breaths per minute, or
   - Pulmonary congestion/oedema with rales or crackles/crepitations at least a third above lung bases; and
3. At least one of the following objective measures:
   - Pulmonary oedema/congestions as shown by chest X-ray, or

- Circulating B-type natriuretic peptide (BNP) concentration of ≥ 400 pg/ml or circulating NT-proBNP concentration of ≥ 1000 pg/ml, or
- A PCWP > 20 mmHg or
- A systolic dysfunction within the last 12 months (EF < 50%) as determined by Trans-Thoracic Echocardiogram (TTE), nuclear testing, cardiac magnetic resonance imaging (MRI) or ventricular angiography).

~~The method utilises a peptide derived from ANP prohormone or a mimetic thereof.~~

It is to be understood that suitable VSDL peptides ~~derived from ANP prohormone include the proANP 1-30, proANP 31-67 and proANP 79-98 peptides of human ANP prohormone described in United States Patent No 5,691,310, as well as derivatives of said peptides such as~~ for use in the present invention include derivatives which include minor variations in the amino acid sequence which do not result in any substantial decrease or variation in biological activity. These variations may include conservative amino acid substitutions such as: Gly, Ala, Val, Ile, Leu, Met; Asp, Glu, Asn, Gln; Ser, Thr; Lys, Arg, His; Phe, Tyr, Trp, His; and Pro, Nα-alkylamino acids; and non-conservative amino acid substitutions. Some specific examples of suitable amino acid substitutions within the ~~ANP prohormone~~ VSDL (pro ANP 1-30) sequence include: Ser→Arg (especially at position 39), Pro→Gln (especially at position 41), Thr→Ala (especially at position 59), Glu→Asp (especially at position 61), and Ser→Asn (especially at position 63).

Suitable mimetics of VSDL ~~a peptide derived from ANP prohormone~~ may be designed using any of the methods well known to the person skilled in the art for designing mimetics of peptides based upon amino acid sequences in the absence of secondary and tertiary structural information[15]. For example, peptide mimetic compounds may be produced by modifying amino acid side chains to increase the hydrophobicity of defined regions of the peptide (eg substituting hydrogens with methyl groups on aromatic residues of the peptides), substituting amino acid side chains with non-amino acid side chains (eg substituting aromatic residues of the peptides with other aryl groups), and substituting amino- and/or carboxy-termini with various substituents (eg substituting aliphatic groups to increase hydrophobicity). Alternatively, mimetic compounds of VSDL ~~a peptide derived from ANP prohormone~~ may be a so-called peptoid (ie non-peptide) which includes modification of the peptide backbone (ie introducing amide bond surrogates by, for example, replacing the nitrogen atoms in the backbone with carbon atoms), or includes *N*-substituted glycine residues, one or more D-amino acids (in place of L-amino acid(s)) and/or one or more α-amino acids (in place of β-amino acids or γ-amino acids). Further, suitable mimetic compounds of VSDL ~~a peptide derived from ANP prohormone~~ include "retro-inverso peptides" where the peptide bonds are reversed and D-amino acids assembled in reverse order to the order of the L-amino acids in the peptide sequence upon which the mimetic is based, and other non-peptide frameworks such as steroids, saccharides, benzazepine 1,3,4- trisubstituted pyrrolidinone, pyridones and pyridopyrazines.

Preferably, the method of the present invention comprises the administration of ~~proANP 31-67 (ie a peptide consisting of the amino acids 31-67 of the ANP prohormone), known as vessel dilator (VSDL),~~ VSDL or a derivative thereof. The amino acid sequence of the preferred, human, VSDL is as follows:

Glu-Val-Val-Pro-Pro-Gln-Val-Leu-Ser-Glu-Pro-Asn-Glu-Glu-Ala-Gly-Ala-Ala-Leu-Ser-Pro-Leu-Pro-Glu-Val-Pro-Pro-Trp-Thr-Gly-Glu-Val-Ser-Pro-Ala-Gln-Arg (SEQ ID NO: 1).

Other suitable VSDL peptides include:

Pongo pygmaeus (common orang-utan)

Glu-Val-Val-Pro-Pro-Gln-Val-Leu-Ser-Glu-Gln-Asn-Glu-Glu-Ala-Gly-Ala-Ala-Leu-Ser-Pro-Leu-Pro-Glu-Val-Pro-Pro-Trp-Thr-Gly-Glu-Val-Ser-Pro-Ala-Gln-Arg (SEQ ID NO: 2);

Macaca mulatta (rhesus monkey)

Glu-Val-Val-Pro-Pro-Gln-Val-Leu-Arg-Glu-Gln-Asn-Glu-Glu-Ala-Gly-Ala-Ala-Leu-Ser-Pro-Leu-Pro-Glu-Val-Pro-Pro-Trp-Thr-Gly-Asp-Val-Ser-Pro-Ala-Gln-Arg (SEQ ID NO: 3);

and

Felis catus

Glu-Val-Val-Pro-Pro-Gln-Val-Leu-Ser-Glu-Gln-Asn-Glu-Glu-Ala-Gly-Ala-Ala-Leu-Ser-Pro-Leu-Pro-Glu-Val-Pro-Pro-Trp-Ala-Gly-Glu-Val-Asn-Pro-Ala-Gln-Arg (SEQ ID NO: 4).

VSDL peptides ~~derived from ANP prohormone~~ may be produced by any of the standard protein synthesis methods well known to the person skilled in the art or, more preferably, by recombinant techniques involving, for example, the introduction of a polynucleotide molecule encoding the particular peptide into a suitable host cell (eg a host cell selected from bacterial cells such as *E. coli*, Streptomyces and *S. typhimurium*; fungal cells such as yeast cells; insect cells such as Drosophila S2 and Spodoptera Sf9 cells; animal cells such as Chinese hamster ovary (CHO), monkey kidney (COS) cells and human embryonic kidney 293 (HEK 293) cells; and plant cells) and culturing the cell under conditions suitable for the expression of the particular peptide.

Preferably, the VSDL ~~peptide derived from ANP prohormone~~ or a mimetic thereof will be administered as a composition consisting of a simple solution or suspension of the peptide or mimetic in a pharmaceutically-acceptable carrier. However, it will be readily appreciated by the person skilled in the art, that the VSDL ~~peptide~~ or mimetic may be bound or associated with a carrier molecule (eg a carrier protein or fusion partner such as human serum albumin (HSA) or a polysaccharide (eg Dextran) or polyether (eg polyethylene glycol)) in order to modulate the biological activity and/or serum half-life time of the peptide or mimetic.

The term "pharmaceutically-acceptable carrier" as used herein refers to any pharmaceutically- or veterinary-acceptable solvent, suspending agent or vehicle for delivering the VSDL ~~peptide derived from ANP prohormone~~ or mimetic thereof to the subject. The carrier may include one or more pharmaceutical additives of a type appropriate to, for example, *iv* administration (eg excipients, preservatives, stabilisers

etc).

The VSDL ~~peptide derived from ANP prohormone~~ or a mimetic thereof may be administered to the subject in a combination therapy. However, while it is considered that the administration of VSDL ~~such a peptide (eg VSDL)~~ or mimetic thereof should not cause clinically significant hypotension, they can be vasodilatory and, therefore, it is preferred that any combination therapy avoids other vasodilatory agents which may cause a synergetic blood pressure lowering. For that reason, the method of the present invention may not be suitable for subjects already using vasodilatory agents.

The administration of VSDL ~~the peptide derived from ANP prohormone~~ or a mimetic thereof by infusion is, preferably, achieved intravenously (*iv*) (which is particularly suitable in the hospital setting) or subcutaneously (*sc*) (which is suitable for both hospitalised patient and out-of-hospital administration). For example, infusion may be via a standard catheter or implantable drug port (eg a Port-a-Cath®; Smiths Medical MD, Inc., St. Paul MN, United States of America), or otherwise achieved using a drug infusion pump (eg implantable drug infusion pumps such as an Alzet® osmotic pump (Durect Corporation, Cupertino CA, United States of America) and a Duros® device (Intarcia Therapeutics, Inc., Hayward CA, United States of America), or a drug infusion pump for subcutaneous (*sc*) administration such as a Paradigm™ device (Medtronic Australasia Pty Ltd, Gladesville NSW, Australia) all of which can provide a controlled release of the peptide or mimetic) which preferably infuses the VSDL ~~peptide~~ or mimetic at a constant rate.

The use of an implantable drug port or drug infusion pump will be particularly well suited for a long term treatment method according to the present invention. Typically, the VSDL ~~peptide~~ or mimetic will be infused at a constant rate, however, in some cases it may be desirable to employ a drug infusion pump employing a feedback control mechanism (eg a feedback linked to measurement of oedema (in the lung) or other surrogate marker) to control release of the VSDL ~~peptide~~ or mimetic.

In one particularly preferred embodiment, the invention provides a method of treating ADCHF in a subject, said method comprising administering to the subject an effective amount of VSDL, wherein said effective amount is in the range of about 0.1 to 20 μg/kg/day and is administered by infusion, preferably intravenous (*iv*) or subcutaneous (*sc*) infusion, at a rate of ≤50 ng/kg/min.

In another particularly preferred embodiment, the invention provides a method of treating ADCHF in a subject, said method comprising administering to the subject an effective amount of VSDL, wherein said effective amount is in the range of about 0.1 to 1.5 μg/kg/day and is administered by infusion, preferably intravenous (*iv*) or subcutaneous (*sc*) infusion.

It will be appreciated by the person skilled in the art that numerous variations and/or routine modifications may be made to the method of the present invention without departing from the spirit or scope of the invention as broadly described. For example, it will be understood that the effective amount and frequency of administration of the VSDL ~~peptide~~ or mimetic for any particular subject may be varied and will depend upon a variety of factors including the activity of the particular VSDL ~~peptide~~ or mimetic that is utilised, the metabolic stability and length of action of the particular VSDL ~~peptide~~ or mimetic, the age, body weight, general health, sex and diet of the particular subject, and the time of administration, rate of excretion, drug combination and severity of the chronic CHF or ADCHF being treated.

The present invention further provides the use of VSDL ~~a peptide derived from atrial natriuretic peptide (ANP) prohormone~~ or a mimetic thereof in the manufacture of a medicament for infusion at a rate of about 1 to 400 ng per kg subject body weight per minute (ng/kg/min), for treating chronic congestive heart failure (CHF) or acute decompensated congestive heart failure (ADCHF) in a subject. In such use, preferably, the medicament is capable of providing an effective amount of the VSDL ~~peptide~~ or mimetic in the range of about in the range of 0.1 to 75 μg/kg/day, but more preferably in the range of about 0.1 to 25 μg/kg/day, still more preferably in the range of about 0.1 to 20 μg/kg/day or about 0.1 to 5 μg/kg/day, and even still more preferably, in the range of about 0.1 to 3.5 μg/kg/day or 0.1 to 1.5 μg/kg/day.

Alternatively, the present invention provides the use of VSDL ~~a peptide derived from atrial natriuretic peptide (ANP) prohormone~~ or a mimetic thereof in the manufacture of a medicament for treating chronic congestive heart failure (CHF) or acute decompensated congestive heart failure (ADCHF) in a subject, wherein said medicament is adapted to provide said subject with an effective amount of VSDL ~~said peptide~~ or mimetic of ≤4.5 μg/kg/day. In such use, preferably, the medicament is capable of providing an effective amount of the VSDL ~~peptide derived from atrial natriuretic peptide (ANP) prohormone~~ or a mimetic in the range of 0.1 to 3.5 μg/kg/day, but more preferably in the range of about 0.1 to 1.5 μg/kg/day.

Most preferably, in the use of the present invention, the medicament is capable of providing an effective amount of the VSDL ~~peptide~~ or mimetic of about 0.75 μg/kg/day.

The medicament may, for example, be adapted for infusion at a rate of < 100 ng/kg/min, and preferably at a rate of about ≤75 ng/kg/min, more preferably at a rate of about ≤50 ng/kg/min or ≤30 ng/kg/min, still more preferably at a rate of about ≤25 ng/kg/min, even still more preferably ≤20 ng/kg/min and, and yet still more preferably at a rate of about ≤15 ng/kg/min. Most preferably, the medicament is adapted for infusion at a rate of about 12.5 ng/kg/min.

The medicament may be used in a single dose per day or administered across multiple times per day (eg 2 to 4 times per day). Typically, a single dose (or each dose of a multidose regimen) will be administered

over a period of about 60 minutes.

Preferably, the medicament is intended for treating the particular indication of ADCHF with a symptom severity level of NYHA class III or IV.

Preferably, the use of the present invention is a use of VSDL or a derivative thereof.

The medicament may be infused intravenously (*iv*) via a standard catheter, implantable drug port or drug infusion pump, or subcutaneously (*sc*) via a drug infusion pump.

In one particularly preferred embodiment, the invention provides the use of VSDL or a mimetic thereof in the manufacture of a medicament for infusion at a rate of ≤50 ng/kg/min, for treating ADCHF in a subject.

In another particularly preferred embodiment, the invention provides the use of VSDL or a mimetic thereof in the manufacture of a medicament for treating ADCHF in a subject, wherein said medicament is adapted to provide said subject with an effective amount of said VSDL ~~peptide~~ or mimetic in the range of about 0.1 to 1.5 μg/kg/day.

The present invention still further provides an infusion device containing, or provided with, a medicament comprising VSDL ~~a peptide derived from atrial natriuretic peptide (ANP) prohormone~~ or a mimetic thereof adapted for infusion at a rate of about 1 to 400 ng per kg subject body weight per minute (ng/kg/min), for treating chronic congestive heart failure (CHF) or acute decompensated congestive heart failure (ADCHF) in a subject.

Alternatively, the present invention provides an infusion device containing, or provided with, a medicament comprising VSDL ~~a peptide derived from atrial natriuretic peptide (ANP) prohormone~~ or a mimetic thereof for treating chronic congestive heart failure (CHF) or acute decompensated congestive heart failure (ADCHF) in a subject, wherein said medicament is adapted to provide said subject with an effective amount of said VSDL ~~peptide~~ or mimetic of ≤4.5 μg/kg/day.

The infusion device may be selected from devices for intravenous (*iv*) infusion (eg a standard catheter, implantable drug port or *iv* drug infusion pump) or subcutaneous (*sc*) infusion (eg *sc* drug infusion pump).

The medicament, which may be as described above, may be contained within a reservoir provided within the device or which may otherwise be operably connected thereto. The arrangement of a connectable reservoir may be such that it is only capable of being reasonably used with the said device.

In one particularly preferred embodiment, the invention provides an infusion device containing, or

provided with, a medicament comprising VSDL adapted for infusion at a rate of ≤50 ng/kg/min, for treating ADCHF in a subject.

In another particularly preferred embodiment, the invention provides an infusion device containing, or provided with, a medicament comprising VSDL adapted to provide said subject with an effective amount of said peptide or mimetic in the range of about 0.1 to 1.5 μg/kg/day, for treating ADCHF in a subject.

In a further aspect, the present invention provides the use of VSDL ~~a peptide derived from atrial natriuretic peptide (ANP) prohormone~~ or a mimetic thereof in the treatment of chronic congestive heart failure (CHF) or acute decompensated congestive heart failure (ADCHF) in a subject, characterised in that the VSDL or mimetic ~~peptide~~ is infused into the subject at a rate of about 1 to 400 ng per kg subject body weight per minute (ng/kg/min).

In a still further aspect, the present invention provides the use of VSDL ~~a peptide derived from atrial natriuretic peptide (ANP) prohormone~~ or a mimetic thereof in the treatment of chronic congestive heart failure (CHF) or acute decompensated congestive heart failure (ADCHF) in a subject, characterised in that the VSDL or mimetic ~~peptide~~ is administered into the subject at an effective amount of ≤4.5 μg/kg/day.

The present invention is hereinafter further described by way of the following, non-limiting example(s).

EXAMPLE(S)

Example 1 Treatment of ADCHF with *iv* administration of vessel dilator

This example describes a study to examine whether VSDL administration to ADCHF patients will be safe and induce improvements in haemodynamic parameters, as well as renal, natriuretic and diuretic parameters, whilst regulating plasma volume and BP within clinically acceptable ranges and without seriously adverse side effects.

Methods and Materials

Formulation

VSDL in the form of a white lyophilised powder (synthesised using standard protein synthesis method by Auspep Pty Ltd, Parkville, VIC, Australia), stored in an ultra low freezer (-80°C), was reconstituted in a vial with 10 ml of 0.9% saline (preservative free) and aseptically transferred into a 20 ml syringe (that conects to a patient cannula) before use.

CLAIMS

1. A method of treating chronic congestive heart failure (CHF) or acute decompensated congestive heart failure (ADCHF) in a subject, said method comprising administering to the subject an effective amount of vessel dilator (VSDL) ~~a peptide derived from atrial natriuretic peptide (ANP) prohormone~~ or a mimetic thereof in the range of about 0.1 to 5 μg/kg/day.

~~2. The method of claim 1, wherein the peptide or mimetic is administered by infusion at a rate of 1 to 400 ng per kg subject body weight per minute (ng/kg/min).~~

~~3. The method of claim 2, wherein the effective amount of the peptide or mimetic is in the range of 0.1 to 75 μg/kg/day.~~

~~4. The method of claim 3, wherein the effective amount of the peptide or mimetic is in the range of about 0.1 to 5 μg/kg/day.~~

~~5~~ 2. The method of claim 1 4, wherein the effective amount of the VSDL ~~peptide~~ or mimetic is in the range of about 0.1 to 3.5 μg/kg/day.

~~6~~ 3. The method of claim 2 ~~5~~, wherein the effective amount of the VSDL ~~peptide~~ or mimetic is about 0.75 μg/kg/day.

~~7~~ 4. The method of any one of claims 1 to 3 ~~6~~, wherein the VSDL ~~peptide~~ or mimetic is administered by infusion at a rate of ≤75 ng/kg/min.

~~8~~ 5. The method of claim 4 ~~7~~, wherein the VSDL ~~peptide~~ or mimetic is administered by infusion at a rate of ≤50 ng/kg/min.

~~9~~ 6. The method of claim 5 ~~8~~, wherein the VSDL ~~peptide~~ or mimetic is administered by infusion at a rate in the range of 1 to 15 ng/kg/min.

~~10. The method of any one of claims 1 to 9, wherein the effective amount of the peptide or mimetic is administered as a single daily dose by infusion over a period of about 60 minutes.~~

~~11. The method of claim 1, wherein the effective amount of the peptide or mimetic is ≤ 4.5 μg/kg/day.~~

~~12~~ 7. The method of claim 1 ~~11~~, wherein the effective amount of the VSDL ~~peptide~~ or mimetic is in the range of 0.1 to 1.5 μg/kg/day.

~~13. The method of claim 12, wherein the effective amount of the peptide or mimetic is about 0.75 μg/kg/day.~~

~~14. The method of any one of claims 11 to 13, wherein the peptide or mimetic is administered by infusion at a rate of ≤ 75 ng/kg/min.~~

~~15~~ 8. The method of claim 7 ~~14~~, wherein the VSDL ~~peptide~~ or mimetic is administered by infusion at a rate of about 25 ng/kg/min.

~~16. The method of claim 15, wherein the peptide or mimetic is administered by infusion at a rate of about 12.5 ng/kg/min.~~

~~17~~ 9. The method of any one of claims 1 to 8 ~~12 to 16~~, wherein the effective amount of the VSDL ~~peptide~~ or mimetic is administered as a single daily dose by infusion over a period of about 60 minutes.

~~18~~ 10. The method of any one of claims 1 to 9 ~~17~~, wherein the method is used for treating chronic CHF with a symptom severity level of NYHA class III.

~~19. The method of any one of claims 1 to 18, wherein the method is used for treating ADCHF with a symptom severity level of NYHA class III or IV.~~

~~20. The method of any one of claims 1 to 19, wherein the method comprises administering vessel dilator (VSDL).~~

~~21. The method of claim 20, wherein the VSDL consists of the amino acid sequence shown as SEQ ID NO: 1.~~

~~22. A method of treating acute decompensated congestive heart failure (ADCHF) in a subject, said method comprising administering to the subject an effective amount of vessel dilator (VSDL), wherein said effective amount is in the range of about 0.1 to 20 μg/kg/day and is administered by infusion at a rate of ≤ 50 ng/kg/min.~~

~~23~~ 11. A method of treating acute decompensated congestive heart failure (ADCHF) in a subject, said method comprising administering to the subject an effective amount of vessel dilator (VSDL),

or a mimetic thereof. ~~wherein said effective amount is in the range of about 0.1 to 1.5 μg/kg/day and is administered by infusion.~~

~~24. An infusion device containing, or provided with, a medicament comprising a peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof adapted for infusion of the peptide or mimetic, for treating chronic congestive heart failure (CHF) or acute decompensated congestive heart failure (ADCHF) in a subject.~~

~~25. A device according claim 24 adapted to infuse the peptide or mimetic at a rate of about 1 to 400 ng per kg subject body weight per minute (ng/kg/min).~~

~~26. A device according to claim 24 or 25 adapted to administer a dose of the peptide or mimetic in the range of 0.1 to 75 μg/kg/day.~~

~~27. A device according to claim 26 adapted to administer a dose of the peptide or mimetic in the range of about 0.1 to 5 μg/kg/day.~~

~~28. A device according to claim 27 adapted to administer a dose of the peptide or mimetic in the range of about 0.1 to 3.5 μg/kg/day.~~

~~29. A device according to claim 28 adapted to administer a dose of the peptide or mimetic of about 0.75 μg/kg/day.~~

~~30. A device according to any one of claims 24 to 29 adapted to infuse the peptide or mimetic at a rate of ≤ 75 ng/kg/min.~~

~~31. A device according to claim 30 adapted to infuse the peptide or mimetic at a rate of ≤ 50 ng/kg/min.~~

~~32. A device according to claim 31 adapted to infuse the peptide or mimetic at a rate in the range of 1 to 15 ng/kg/min.~~

~~33. A device according to any one of claims 24 to 32 adapted to infuse the peptide or mimetic as a single daily dose over a period of about 60 minutes.~~

~~34. A device according to claim 24 adapted to administer a dose of the peptide or mimetic of ≤ 4.5 μg/kg/day.~~

~~35. A device according to claim 34 adapted to administer a dose of the peptide or mimetic in the range of 0.1 to 1.5 μg/kg/day.~~

~~36. A device according to claim 35 adapted to administer a dose of the peptide or mimetic of about 0.75 μg/kg/day.~~

~~37. A device according to any one of claims 34 to 36 adapted to infuse the peptide or mimetic at a rate of ≤ 75 ng/kg/min.~~

~~38. A device according to claim 37 adapted to infuse the peptide or mimetic at a rate of about 25 ng/kg/min.~~

~~39. A device according to claim 38 adapted to infuse the peptide or mimetic at a rate of about 12.5 ng/kg/min.~~

~~40. A device according to any one of claims 34 to 39 adapted to infuse the peptide or mimetic as a single daily dose over a period of about 60 minutes.~~

~~41. The device of any one of claims 24 to 40, wherein the medicament is contained within a reservoir provided within the device or which is otherwise operably connected thereto~~.

12. The method of claim 11, wherein the VSDL or mimetic is administered by infusion at a rate of 1 to 400 ng per kg subject body weight per minute (ng/kg/min).

13. The method of claim 12, wherein the effective amount of the VSDL or mimetic is in the range of 0.1 to 75 μg/kg/day.

14. The method of claim 11, wherein said effective amount is in the range of about 0.1 to 20 μg/kg/day and is administered by infusion at a rate of ≤50 ng/kg/min.

15. The method of claim 11, wherein said effective amount is in the range of about 0.1 to 1.5 μg/kg/day and is administered by infusion.

16. The method of any one of claims 1 to 15, wherein the method comprises administering vessel dilator (VSDL).

17. The method of claim 16, wherein the VSDL consists of the amino acid sequence shown as SEQ ID NO: 1.