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CA 2416754 C 2007/12/18

(11)(21) **2 416 754**

(12) **BREVET CANADIEN
CANADIAN PATENT**

(13) **C**

(86) Date de dépôt PCT/PCT Filing Date: 2001/06/27

(87) Date publication PCT/PCT Publication Date: 2003/01/24

(45) Date de délivrance/Issue Date: 2007/12/18

(85) Entrée phase nationale/National Entry: 2003/01/24

(86) N° demande PCT/PCT Application No.: JP 2001/005508

(87) N° publication PCT/PCT Publication No.: 2002/007735

(30) Priorité/Priority: 2000/07/26 (JP2000-225330)

(51) Cl.Int./Int.Cl. *A61K 33/06* (2006.01),
A61K 31/7016 (2006.01), *A61K 33/00* (2006.01),
A61K 33/14 (2006.01), *A61P 9/00* (2006.01)

(72) Inventeurs/Inventors:

KOMEDA, MASASHI, JP;
MIWA, SENRI, JP;
WADA, HIROMI, JP

(73) Propriétaire/Owner:

FUSO PHARMACEUTICAL INDUSTRIES, LTD., JP

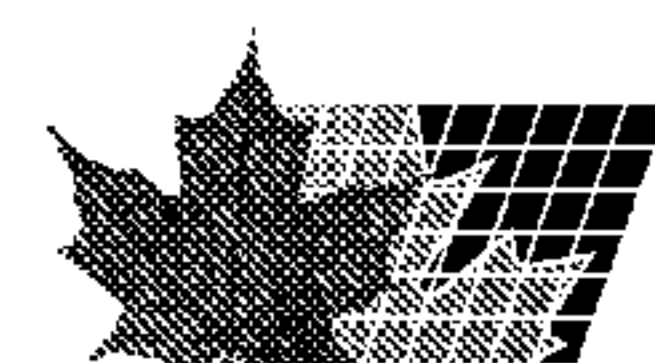
(74) Agent: R. WILLIAM WRAY & ASSOCIATES

(54) Titre : LIQUIDE CONTRE L'ARRET CARDIAQUE

(54) Title: CARDIAC ARREST FLUID

(57) Abrégé/Abstract:

A cardioplegic solution which contains a trehalose and one or more metal ions. The trehalose is preferably contained in an amount of not more than 3.5% (W/V), or 1.5 to 3.5% (W/V). The metal ions are preferably Na⁺, K⁺, Mg⁺⁺ and Ca⁺⁺. The cardioplegic solution is useful for cardiac standstill and cardiac muscle protection.



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ABSTRACT

A cardioplegic solution which contains a trehalose and one or more metal ions. The trehalose is preferably contained in an amount of not more than 3.5% (W/V), or 1.5 to 3.5% (W/V).
5 The metal ions are preferably Na⁺, K⁺, Mg⁺⁺ and Ca⁺⁺. The cardioplegic solution is useful for cardiac standstill and cardiac muscle protection.

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SPECIFICATION

CARDIAC ARREST FLUID

5 Technical Field

The present invention relates to a cardioplegic solution.

Background Art

10 In heart surgery, the heart needs to be subjected to artificial cardiac standstill by perfusing the heart with a cardioplegic solution. In addition, during cardiac standstill, the cardiac muscle is in a state of ischemia resulting in a lack of oxygen, which is likely to reduce heart
15 functions. Thus, a cardioplegic solution must be provided with a function of protecting the heart muscle in addition to the action of stopping the heart. Conventionally known cardioplegic solutions include the St. Thomas solution. The St. Thomas solution contains a variety of metal ions such as
20 Na^+ , K^+ , Mg^{++} , and Ca^{++} , and the concentration of each ion is close to that of the extracellular fluid.

However, conventional cardioplegic solutions do not have a sufficient action of protecting the cardiac muscle.

Hence, the object of the present invention is to provide
25 a cardioplegic solution useful for cardiac standstill and cardiac muscle protection.

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Disclosure of the Invention

The present inventors have conducted intensive studies and completed a cardioplegic solution of the present invention, which contains trehalose and metal ions. A cardioplegic solution of the present invention is provided with an excellent action of protecting the cardiac muscle in comparison with the conventional ones.

As trehalose, any of α,α -trehalose, α,β -trehalose, and β,β -trehalose may be used. Desirably, α,α -trehalose present in nature is used. A preferred content of trehalose is 3.5% (w/v) or less, and a more preferred content is from 1.5 to 3.5% (w/v).

Desirable metal ions that are made contained in a cardioplegic solution of the present invention include Na^+ , K^+ , Mg^{++} , and Ca^{++} , because they induce a sudden heart stop or prevent the inflow of extracellular metal ions into the inside of the cell while maintaining the balance with the extracellular fluid. Regarding preferred contents of these, Na^+ is from 100 to 140 mmol/L, K^+ is from 10 to 20 mmol/L, Mg^{++} is from 5 to 40 mmol/L, and Ca^{++} is from 0.5 to 3 mmol/L. Also, addition of electrolytes such as NaCl, KCl, $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$, and $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ is appropriate in order to render these metal ions to be contained therein.

The pH of a cardioplegic solution of the present invention is desirably in the range of 7.4 to 7.8, which is

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close to the range of the extracellular fluid. To adjust the pH to this range, addition of a suitable amount of, for example, NaHCO_3 is appropriate.

5 Best Mode for Carrying out the Invention

- Examples -

NaCl , KCl , $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$, $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$, and α, α -trehalose are dissolved in water and then to this was added water to totally 100 mL. Thereafter, to the resulting solution was added 1 mL of an 8.4% (w/v) NaHCO_3 solution to prepare Example Solutions 1 to 3 indicated in Table 1. In addition, a St. Thomas solution was prepared in a similar manner except using no α, α -trehalose. Additionally, the contents in Table 1 express the values measured prior to the addition of the NaHCO_3 solution.

[Table 1]

		Thomas solution	Example Solution 1	Example Solution 2	Example Solution 3
Attributes	Color and clarity	Colorless and clear 294	Colorless and clear 358	Colorless and clear 390	Colorless and clear 427
	Osmotic pressure (mOsm/kg)				
	Transmittivity (%)	100.0	100.0	100.0	100.0
	pH	7.80	7.43	7.44	7.78
Contents	Na ⁺ (mmol/l)	112.6	110.4	110.0	112.7
	K ⁺ (mmol/l)	16.3	15.8	15.7	16.4
	Ca ⁺⁺ (mmol/l)	1.12	1.18	1.16	1.12
	Mg ⁺⁺ (mmol/l)	16.3	15.5	15.7	16.3
	Cl ⁻ (mmol/l)	161.8	161.0	161.4	162.1
	Trehalose (w/v%)	-	2.03	3.01	4.16
Insoluble foreign matter	Not observed	Not observed	Not observed	Not observed	Not observed

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- Test Example 1 -

SD rats (male) with weights of 300 to 400 g are divided into two groups (Group A and Group B), each having 9 rats, and then are subjected to the cardiac standstill test below. In addition, as the cardioplegic solution, the St. Thomas solution was used for Group A and Example Solution 2 was used for Group B.

First, each rat was anesthetized with ether and subjected to median thoractomy. Then, the heart was removed and immediately immersed in an ice cooled Krebs-Henseleit Buffer (NaCl 0.6895 g, KCl 0.0343 g, MgSO₄ 0.145 g, CaCl₂·2H₂O 0.368 g, KH₂PO₄ 0.164 g, NaHCO₃ 2.10 g, Glucose 0.188 g/100 mL). Immediately after the weight measurement, the heart was placed in the Langendorff apparatus and then was subjected to preliminary perfusion using Krebs-Henseleit Buffer (saturated with a mixture gas of O₂ (95%) and CO₂ (5%)) as the perfusion solution. Thereafter, a latex balloon was inserted at the left atrium into the left ventricle by way of the mitral valve and further was connected to a pressure monitor via a transducer. After 20-minute preliminary perfusion, the balloon was made expanded in the left ventricle for pressure measurement, thereby evaluating the pressure-volume relationship.

Next, the heart was made stopped by perfusion of 20 mL/kg of a cardioplegic solution cooled to 4°C. The cardioplegic solution was added by 10 mg/kg every 30 minutes. After the cardiac standstill was kept for 90 minutes, the

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Krebs-Henseleit Buffer (saturated with a mixture gas of O₂ (95%) and CO₂ (5%)) was re-perfused as the perfusion solution.

Then, at a lapse of 5 minutes after the initiation of the re-perfusion, a pressure-volume relationship was evaluated in the same manner as the above, with the ratio of the value after to the value before, the cardiac standstill, calculated. In addition, the weight of the cardiac muscle was measured to evaluate the weight increase ratio relative to the value prior to the cardiac standstill and further the cardiac muscle was observed pathologically.

As a result, the ratios of the end-diastolic pressure-volume relationship (EDPVR) values to the values prior to the cardiac standstill were 1.59 ± 0.90 for Group A and 3.45 ± 1.16 for Group B, indicating that there is no significant difference between the two groups ($P = 0.13$). However, regarding the end-systole pressure-volume relationship (ESPVR), the ratios were 0.71 ± 0.07 for Group A and 0.98 ± 0.05 for Group B, indicating that the value of Group B is significantly better ($P < 0.05$). This shows that Example Solution 2 is superior in the action of maintaining cardiac muscle systole ability to the St. Thomas solution.

Furthermore, the weight increase ratios of the cardiac muscle relative to the value prior to the cardiac standstill were 1.46 ± 0.71 for Group A and 1.14 ± 0.37 for Group B, showing that Group B significantly indicates a smaller value ($P < 0.001$). This shows that Group B has a fewer occurrences of

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edema. In addition, pathological observation also shows that Group B tends to have a fewer occurrences of edema. This proves that Example Solution 2 is better in action of suppressing edema than the St. Thomas solution.

5 Consequently, Example Solution 2 is shown to be superior in action of cardiac muscle protection to the St. Thomas solution. Table 1 shows that Example Solution 2 has almost the same composition as that of the St. Thomas solution except containing trehalose. Therefore, the test results show that
10 trehalose has an excellent action of protecting the cardiac muscle.

- Test Example 2 -

SD rats (male) with weights of 300 to 400 g are divided
15 into three groups (Group a, Group b and Group c), each having 7 rats. Then, in a manner similar to Test Example 1 above, the heart of each rat was made stopped and subjected to re-perfusion. The ratios of the pressure-volume relationship relative to the value prior to cardiac standstill were
20 evaluated at lapses of 5 minutes and 15 minutes after the initiation of the re-perfusion. In addition, regarding cardioplegic solutions, Example Solution 1 was used for Group a, Example Solution 2 for Group b, and Example Solution 3 for Group c.

25 As a result, the ratios of the end-systole pressure-volume relationship were found to have no significant

differences between the three groups at lapses of both 5 minutes and 15 minutes. The ratios of the end-diastolic pressure-volume relationship, at a lapse of 15 minutes, were 1.67 $\pm$ 1.07 for Group a, 1.88 $\pm$ 0.65 for Group b, and 1.74 $\pm$ 1.23 for Group c, which show no significant differences as well. However, the ratios, at a lapse of 5 minutes, were 3.25 $\pm$ 1.43 for Group a, 3.45 $\pm$ 1.16 for Group b, and 5.74 $\pm$ 2.88 for Group c, with the value of Group c being inferior to those of the other two groups. In other words, Group c has a slow recovery of the cardiac muscle diastole ability as compared with the other two groups. This shows that Example Solutions 1 and 2 are superior in action of maintaining the cardiac muscle diastole ability to Example Solution 3. In addition, Table 1 indicates that the osmotic pressure values of Example Solutions 1 and 2 are as good as 358 and 390 mOsm/kg, respectively, while the value of Example Solution 3 is as high as 427 mOsm/kg.

Consequently, Example Solutions 1 and 2 are more appropriate as the cardioplegic solution than Example Solution 3. Table 1 indicates that Example Solutions 1, 2, and 3 contain, respectively, about 2, about 3, and about 4.1% (w/v) of trehalose, and they have almost the same composition excluding the concentrations of trehalose. Thus, the test results suggest that a suitable concentration of trehalose in a cardioplegic solution is from about 1.5 to about 3.5% (w/v).

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Industrial Applicability

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A cardioplegic solution of the present invention is provided with excellent actions of maintaining heart function and of suppressing edema, and thus is useful for cardiac standstill and cardiac muscle protection.

CLAIMS

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A cardioplegic solution, the solution containing a trehalose in an amount of 1.5 to 3.5% (W/V), Na^+ in an amount of 100 to 140 mmol/L, K^+ in an amount of 10 to 20 mmol/L, Mg^{++} in an amount of 5 to 40 mmol/L and Ca^{++} in an amount of 0.5 to 3 mmol/L.
2. The cardioplegic solution according to claim 1, wherein the trehalose is α , α -trehalose.
3. The cardioplegic solution according to claim 1 or claim 2, wherein each metal ion of Na^+ , K^+ , Mg^{++} and Ca^{++} is derived from an electrolyte.
4. The cardioplegic solution according to any one of claims 1, 2, or 3, wherein the solution has a pH of 7.4 to 7.8.

R. WILLIAM WRAY & ASSOCIATES

BOX 2760 - STATION D

OTTAWA, CANADA K1P 5W8

PATENT AGENT FOR THE APPLICANT