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3,577,522

METHODS FOR THE TREATMENT OF SHOCK WITH ETHYLENE OXIDE-POLYPROPYLENE GLYCOL CONDENSATES AS BLOOD PLASMA SUBSTITUTES

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No Drawing. Continuation-in-part of application Ser. No. 762,633, Sept. 25, 1968, which is a continuation-in-part of application Ser. No. 670,408, Sept. 25, 1967. This application Oct. 10, 1969, Ser. No. 865,521

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5 Claims

ABSTRACT OF THE DISCLOSURE

Isotonic solutions of certain ethylene oxide-polypropylene glycol condensation products have been found to be extremely effective as blood plasma substitutes in the treatment of shock.

This application is a continuation-in-part of copending U.S. patent application Ser. No. 762,633 filed Sept. 25, 1968, now abandoned, which is in turn a continuation-in-part of U.S. patent application Ser. No. 670,408 filed Sept. 25, 1967, now abandoned.

The present invention relates to a method for the treatment of shock. More particularly, the invention relates to the use of certain solutions of ethylene oxide-polypropylene glycol condensation products as blood plasma substitutes in the treatment of shock.

Shock may be defined as the failure to profuse blood through the capillaries of organs. It is often caused by the loss of excessive amounts of blood. It is well known that of utmost immediate concern in the treatment of shock is the control of the circulating blood volume. Since the body has lost blood, it is necessary in the treatment of shock that either blood or a blood substitute be immediately injected into the body in shock.

Because of the high cost and scarcity of blood plasma, the art has long been in need of a material which will perform as a substitute therefor. To be useful as a blood plasma substitute, a material must possess the following properties: (1) it must retain a sufficient molecular size to remain in the blood space, thus creating an osmotic pressure great enough to retain the solvent (water) within the circulation, (2) it must be miscible with blood, (3) it must be nonantigenic, nontoxic and nonpyretogenic, (4) it must not draw water from the cellular area of the body, (5) it must be readily available and stable under prolonged storage conditions, and (6) when no longer needed, it must be readily discharged from the body circulation. With such formidable requirements, it is little wonder that the art has not heretofore found any material which satisfactorily performs as a blood plasma substitute. This is so notwithstanding the fact that various materials such as salt solutions, gelatin derivatives, various proteins and derivatives thereof, mannitol, starch and dextrans have been investigated as blood plasma substitutes. However, these materials all lack one or more of the above requirements, thereby rendering them not totally acceptable as blood plasma substitutes.

Now, in accordance with the present invention, it has been determined that certain solutions of ethylene oxide-polypropylene glycol condensation products may be effectively employed as blood plasma substitutes in the treatment of shock. It has been determined that by the process of the present invention, the circulating blood volume of the body may be quickly and effectively restored without any subsequent injurious effect on the body system. Thus, the process of the present invention com-

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prises the improvement in the treatment of shock which comprises employing as a blood or blood plasma substitute, an isotonic (isosmotic) solution containing from 0.375 to 1.5 millimoles/liter of a compound of the formula



wherein a is an integer such that the hydrophobe base represented by $(\text{C}_3\text{H}_6\text{O})_a$ has a molecular weight of from 950 to 4000, preferably from 1750 to 4000, and b is an integer such that the hydrophilic portion represented by $(\text{C}_2\text{H}_4\text{O})_b$ constitutes from about 50% to 90% by weight of the compound. By the phrase "isotonic or isosmotic solution" is meant a solution having the same osmotic pressure as blood. This phrase is well known in the art. Illustrative solutions which may be employed in the preparation of the blood plasma substitutes employed in the process of the present invention include saline (a solution of sodium chloride, containing 8.5 to 9.5 grams of salt in 1000 cc. of purified water), Ringer's solution, lactated Ringer's solution, Krebs-Ringer's solution, and various sugar solutions.

As stated above, critical amounts of certain ethylene oxide-polypropylene glycol condensation products must be employed in the preparation of the blood plasma substitutes useful in the present invention. Generally, the isotonic solutions useful in the present invention will comprise from 0.375 to 1.5 millimoles/liter of the above-mentioned ethylene oxide-polypropylene glycol condensation products. Compositions comprising amounts of products outside of the above-cited range have been found to be unacceptable blood plasma substitutes. Although it is not a preferred manner of carrying out the method of the present invention, compositions comprising high concentrations of the above condensation product may be employed in the treatment of shock by injecting small amounts of these compositions into the body circulation. By this procedure, water is drawn from the body into the circulation, thus diluting the compositions. The net effect is the employment of compositions containing the concentrations of ethylene oxide-polypropylene glycol condensation products within the range cited above. Thus, the blood plasma substitutes of the present invention are employed by parenteral injection, preferably intravenous injection, into a body in shock.

The condensation products which are operable in the present invention are prepared by condensing ethylene oxide with polypropylene glycol. A more detailed discussion of the preparation of these products is found in U.S. 2,674,619. To be useful in the present invention, the products must contain at least 50% by weight of ethylene oxide. Furthermore, the polypropylene glycol base must have a molecular weight of at least 950. It has been determined that products outside of these limits are not satisfactory blood plasma substitutes for various reasons. For example, a product containing less than 50% ethylene oxide is not sufficiently nontoxic to be useful whereas a product containing a hydrophobic base molecular weight of less than about 950 has completely different physical properties, particularly with regard to solubility, than the products useful in the present invention.

Illustrative ethylene oxide-polypropylene glycol condensation products which may be employed in the preparation of the isotonic solutions useful in the present invention include:

- (1) 4750 molecular weight polyol containing approximately 80% by weight ethylene oxide,
- (2) 3500 molecular weight polyol containing approximately 50% by weight ethylene oxide,
- (3) 7800 molecular weight polyol containing approximately 80% by weight ethylene oxide,

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- (4) 7500 molecular weight polyol containing approximately 70% by weight ethylene oxide,
- (5) 16,250 molecular weight polyol containing approximately 80% by weight ethylene oxide,
- (6) 13,330 molecular weight polyol containing approximately 70% by weight ethylene oxide,
- (7) 9500 molecular weight polyol containing approximately 90% by weight ethylene oxide

The following examples illustrate the nature of the invention. All parts are by weight unless otherwise stated.

EXAMPLE I

An isotonic solution was prepared by dissolving 0.4% by weight of a 7800 molecular weight polyol prepared by condensing ethylene oxide with a polypropylene glycol having a molecular weight of 1750, said polyol containing approximately 80% ethylene oxide in lactated Ringer's solution (0.513 millimole/liter). Ringer's lactated is a solution of 570 to 630 mg. sodium chloride, 290 to 330 mg. sodium lactate, 18 to 22 mg. calcium chloride, and 27 to 33 mg. potassium chloride in each 100 cc. of distilled water. The solution was then tested as a blood plasma substitute in the treatment of mongrel dogs in hemorrhagic shock.

Twelve dogs were subjected to hemorrhagic shock in a standardized manner as described by Wiggins and modified by Moyer et al., Archives of Surgery, volume 93, page 537, October 1966, "A Bioassay of Treatment of Hemorrhagic Shock." A group of four of these dogs was treated by returning all blood withdrawn plus two times the amount of blood withdrawn of the above salt solution. All four dogs survived without any complications. A group of eight of these dogs was treated by simply returning all blood withdrawn. Three of these dogs survived without any complications while the other five dogs expired.

EXAMPLE II

A solution containing 1.0 millimole/liter of a polyol having a molecular weight of about 16,250 and containing approximately 80% ethylene oxide prepared by the reaction of ethylene oxide with a polypropylene glycol having a molecular weight of 3250 was prepared by dissolving 16.25 grams of said polyol in 10 liters of saline solution containing 9 grams of sodium chloride in 1000 cc. of water. The solution is then employed in the manner described in Example I. Results similar to those of Example I are obtained.

EXAMPLE III

An isotonic solution was prepared by dissolving 0.4% by weight of a 7800 molecular weight polyol prepared by condensing ethylene oxide with a polypropylene glycol having a molecular weight of 1750, said polyol containing approximately 80% ethylene oxide in lactated Ringer's solution (0.513 millimole/liter). Ringer's lactated is a solution of 570 to 630 mg. sodium chloride, 290 to 330 mg. sodium lactate, 18 to 22 mg. calcium chloride, and 27 to 33 mg. potassium chloride in each 100 cc. of distilled water. The solution was then tested as a blood plasma substitute in the treatment of male beagle dogs, six to eight months of age in hemorrhagic shock.

Seventy-five dogs were subjected to hemorrhagic shock in a standardized manner as described by Wiggins and modified by Moyer et al., Archives of Surgery, volume 93, page 537, October 1966, "A Bioassay of Treatment of Hemorrhagic Shock." Moyer's method was further modified in the following manner: (1) all animals were preinfused with normal saline (25 ml./kilogram), 30 to 60 minutes prior to onset of hemorrhage; (2) the period of shock was at a mean arterial blood pressure of 75 mm. mercury for 90 minutes. At the end of this two-hour period, the animal was randomized for treatment in the manner described below.

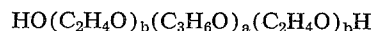
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A group of 25 of these dogs was treated by returning all blood withdrawn. Five of these dogs survived (20% survival). A group of 26 of these dogs was treated by returning all blood withdrawn plus two times the amount of blood withdrawn of lactated Ringer's solution. Eleven of these dogs survived (42% survival). A group of 24 of these dogs was treated by returning all blood withdrawn plus two times the amount of blood withdrawn of the above-described isotonic solution. Sixteen of these dogs survived (67% survival).

While the above examples specifically illustrate the treatment of dogs in accordance with the process of the present invention, it is to be understood that the invention is applicable to all living animal bodies. Representative of such living animal bodies are domestic animals such as dogs cats; farm animals such as horses, cows, and pigs; and wild animals such as chimpanzees and monkeys.

What is claimed is:

1. A method for the treatment of shock which comprises injecting into a body in shock as a blood plasma substitute an isotonic solution containing from 0.375 to 1.5 millimoles/liter of a compound of the formula



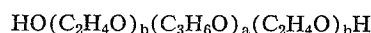
wherein a is an integer such that the hydrophobe base represented by $(\text{C}_3\text{H}_6\text{O})_a$ has a molecular weight of 950 to 4000 and b is an integer such that the hydrophile portion represented by $(\text{C}_2\text{H}_4\text{O})_b$ constitutes from about 50% to 90% by weight of the compound.

2. The method of claim 1 wherein the isotonic solution comprises from 0.375 to 1.5 millimoles/liter of a compound of the formula



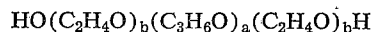
wherein a is an integer such that the hydrophobe base represented by $(\text{C}_3\text{H}_6\text{O})_a$ has a molecular weight of from 1750 to 4000.

3. The method of claim 1 wherein the isotonic solution comprises from 0.375 to 1.5 millimoles of a compound of the formula



wherein a is an integer such that the hydrophobe base represented by $(\text{C}_3\text{H}_6\text{O})_a$ has a molecular weight of 950 to 4000 and b is an integer such that the hydrophile portion represented by $(\text{C}_2\text{H}_4\text{O})_b$ constitutes from about 50% to 90% by weight of the compound per liter of lactated Ringer's solution.

4. The method of claim 1 wherein the isotonic solution comprises from 0.375 to 1.5 millimoles of a compound of the formula



wherein a is an integer such that the hydrophobe base represented by $(\text{C}_3\text{H}_6\text{O})_a$ has a molecular weight of 950 to 4000 and b is an integer such that the hydrophile portion represented by $(\text{C}_2\text{H}_4\text{O})_b$ constitutes from about 50% to 90% by weight of the compound per liter of saline solution.

5. The method of claim 1 wherein the isotonic solution is intravenously injected into a body in shock.

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