PATENT SPECIFICATION (11) 1 582 992

1 582 992

(21) Application No. 31761/77 (22) Filed 28 Jul 1977

(31) Convention Application No. 709342 (32) Filed 28 Jul 1976 in

(33) United States of America (US)

(44) Complete Specification Published 21 Jan 1981

(51) INT.CL.[3] A61K 31/185

(52) Index at Acceptance A5B 180 20Y 230 23Y 26Y 272 27X 27Y 316 31Y 36X 36Y 390 391 401 40Y H

(72) Inventor: Roger Lee Stone

(54) INTRAVENOUS SOLUTIONS WITH AN ANTIMICROBIAL AGENT

(71) We, THE PROCTER & GAMBLE COMPANY, a corporation organised under the laws of the State of Ohio, United States of America, of 301 East Sixth Street, Cincinnati, Ohio 45202, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:–

The present invention relates to a method of treating a composition adapted for intravenous administration, in order to inhibit the growth of microbes therein. The invention also relates to compositions so treated, and to their use.

The present invention is applicable to intravenous solutions or dispersions used in the medical and veterinary arts, especially those used for parenteral nutrition.

The administration of intravenous solutions of various types to humans and lower animals is indicated in the treatment of a variety of disease states. For the most part, the use of such solutions under appropriate, sterile conditions is carried out without harmful side effects. However, it is now becoming recognized that prolonged administration of intravenous solutions, which involves repeated changes of exhausted solution reservoirs, removal and re-insertion of catheters, and other physical manipulations and adjustments of the intravenous apparatus, can lead to whole body mycotic and/or bacterial infections if sterile conditions are not rigorously maintained.

Fungi constitute a class of ubiquitous microorganisms. For the most part, the common fungi are non-pathogenic to humans and lower animals unless they somehow become introduced into the bloodstream. Once in the bloodstream, a massive fungal infestation throughout the body can result. Unfortunately, mycotic (fungal, mold, yeast) infections, which are typically occasioned by extremely high fevers, are unusually refractive to standard therapeutic agents used to combat bacterial infections and often result in death of the patient.

Fungal infestation is now becoming recognized as a particularly troublesome problem associated with the administration of intravenous solutions. As noted, this problem becomes especially acute during the course of a regimen of total parenteral nutrition, wherein repeated changes of the nutrient reservoir, and repeated manipulations of the catheters and apparatus, etc., are involved. In point of fact, medical progress in developing new treatment regimens for burn victims, comatose patients, patients who have undergone gastrointestinal surgery, and other patients who require total parenteral nutrition, has been hindered by this problem.

Moreover, it will be appreciated that nutrient solutions designed to provide parenteral nutrition to humans and lower animals also constitute optimal growth media for fungi. Indeed, some fungi can even exist in concentrated electrolyte solutions, such as the saline solutions typically used medically as irrigants. Intravenous solutions designed for total parenteral nutrition, and which contain a nitrogen source (typically, protein hydrolysates) and/or an energy source (typically, sugars) are especially good growth media for fungi.

As will be recognized from the foregoing, spillage, seepage, or other exposure of sterile intravenous solutions to non-sterile conditions increases the chance that fungal contamination and growth will occur. Once the fungi are established on or around the intravenous apparatus or on the site of infusion into the patient's vein, contamination of the bloodstream becomes a high risk probability for the patient.

Similarly, it has been demonstrated that as much as 10% of hospital i.v. solutions become contaminated by bacteria during use.

By the present invention, antimicrobial agents are used to prevent mycotic and bacterial infections in patients receiving intravenous solutions. It is to be understood that the use of antimicrobials in the manner of this invention is prophylactic (i.e., to prevent mycotic or bacterial infection) rather than therapeutic (i.e., to cure an established disease).

The preferred agents herein can be used at least as a partial substitute for the heat- or filtration-sterilization procedures normally used

in the manufacture of intravenous solutions and provide sterility even during use situations where sterility is usually lost.

The use of various fungistats to inhibit the growth of fungi and molds in food compositions is well known. For example, sodium propionate is routinely added to commercial bread to inhibit the growth of fungi and molds.

The Doctoral Dissertation of Roger L. Stone, entitled, THE REQUIREMENTS FOR METABOLIZABLE ENERGY AND NITROGEN FOR MAINTENANCE IN PARENTERALLY FED SHEEP, The Ohio State University, published August, 1975, p. 37, discloses the use of propionic acid in intravenous solutions.

U.S. Patent 2,154,449, to Hoffman, et al., 1939, describes the use of aliphatic carboxylic acids (C_3 - C_{12}) or their salts as mold inhibitors in foods, The patent teaches the use of these acids to protect materials susceptible to mold, including tobacco, paper, leather, textiles, etc.

U.S. Patent 2,190,714, to Hoffman, et al., 1940, claims a method of inhibiting mold growth in food products other than margarine and sourdough bread by adding a C_3 - C_{12} carboxylic acid thereto.

U.S. Patent 3,404,937, to Kooistra and Troller, 1968, discloses and claims an antimicrobial composition containing 1-10 parts by weight of an edible mineral salt (iron, manganese, zinc, tin or silver) and 1-150 parts by weight of an edible acid preservation substance, specifically including propionic acid. The metal salts are taught to impart enhanced and sustained antimicrobial/antifungal activity to the acid preservation substance.

U.S. Patent 1,772,975, Wieland, 1930, teaches the use of solutions of lactic acid, acetic acid, or homologs thereof, as antiseptics at properly adjusted pH's.

U.S. Patent 2,466,663, Russ, et al., 1949, describes the use of caprylic (octanoic) acid to combat mycotic infections or growths. This acid may be used topically as a liquid, ointment or powder for the treatment of surface infections. It is also taught to be useful for combating internal infections by injecting, intravenously, solutions of the acid and its salts at the pH of blood.

THE MERCK INDEX, Seventh Edition, page 1117, teaches that zinc propionate is used as a fungicide on adhesive tape to reduce plaster irritation caused by molds, fungi and bacterial action. MERCK, at page 860, teaches that propionic acid, and propionates, e.g., sodium, zinc and calcium propionates, are used as mold inhibitors and preservatives and as topical fungicides in the form of ointments or powders.

Mycotic infections associated with the administration of intravenous solutions are generally attributed to some species of *Candida*, especially *C. albicans*. The effect of various fungistats on *Candida* has been reported in the literature.

The inhibition of the growth of *C. albicans in vitro* by propionic acid has been reported by Carpenter, ANTIBIOTICS AND CHEMOTHERAPY V, No. 5, May, 1955, 255, 259.

Propionates and butyrates have been injected into animals in metabolic studies and for the relief of hyperglycemia conditions. B.J. Potter, NATURE, No. 4326, 9/27/52 at 541 and R.M. Cook, *Biochim. et Biophys. Acta*, 201 (1970) 91-100.

A comparison of the bacteriostatic and fungistatic properties of propionic acid and caprylic acid was made by A. Georges, *Arch. belges. Derm. Syph.* 1953, 9/1 (1-13), who concluded that the fungistatic properties of the latter compound are greater than the former.

French Brevet Special de Medicament 8.058M, July, 1970, Appl. 148,347, April 17, 1968, Jean-Pierre Durlach, discloses vitamin B_6 compositions containing magnesium propionate, magnesium lactate, and propionic acid to adjust pH. The compositions are said to be useful orally or parenterally for vitamin B_6 thereapy.

As can be seen from the foregoing, the use of various materials to control fungi in non-sterile dry food systems is well known in the art. However, the advantages of co-administering fungistatic agents with intravenous solutions does not appear to have been recognized heretofore. Apparently, medical researchers have tacitly assumed that the sterilized solutions used for intravenous feeding remain sterile in use. Accordingly, there has been no rationale for using fungistats in the manner of this invention.

The present invention provides a method of treating a composition, adapted for intravenous administration and being a saline solution or comprising a nutritive substance and pyrogen-free water, in order to inhibit the growth of microbes therein, which method comprises the inclusion, as an antimicrobial agent, of a water-soluble, pharmaceutically acceptable, C_4 - C_{12} carboxylic acid and/or a water-soluble, pharmaceutically acceptable salt thereof, in an amount such that the concentration of the acid and/or salt thereof is from 0.01 to 10% by weight.

The invention also provides a composition adapted for intravenous administration and comprising a nutritive substance and pyrogen-free water, which composition has been treated by such a method.

The invention also provides a process for providing parenteral nutrition to a non-human animal, which comprises administering intravenously to said animal such a nutrient composition. In one embodiment the antimicrobial agent is incorporated into the composition concurrently with the intravenous administration.

The present invention encompasses compositions and processes useful in the medical and veterinary arts for providing parenteral nutrition to a human or lower animal with minimal incidence of bacterial or mycotic infection.

The compositions herein are administered intravenously to provide a nutritious amount of a nutritive substance to the patient and are suitable for use over a prolonged treatment regimen.

By "nutritious amount" herein is meant an amount of a material sufficient to furnish or sustain life, i.e., to feed.

By "nutritive substance" herein is meant a food substance suitable to meet the metabolic requirements of a human or lower animal. More particularly, the nutritive substances herein comprise energy sources such as sugars; nitrogen sources such as proteins, polypeptides, amino acids, or mixtures thereof, which are commonly found in protein hydrolysates; mixtures of sugars and nitrogen sources; and lipid dispersions known in the art for intravenous administration. Vitamins and minerals are not included in the term "nutritive substance" as employed herein, but such materials can optionally be present in the compositions of this invention.

By "sugar" herein is meant the saccharidic materials which can be metabolized by humans and lower animals and employed as an energy source. Dextrose is highly preferred for this use.

By "amino acid source" herein is meant a substance that is, or is metabolized into, an amino acid, in particular a protein, polypeptide, amino acid, or protein hydrolysate which is sufficiently water soluble to be incorporated in nutritious amounts in an aqueous solution.

By "fungi" herein is meant the higher protists, including the phycomycetes, the ascomycetes and basidiomycetes, as well as other protista commonly referred to as "yeasts" or "molds". As noted hereinabove, *Candida*, especially *Candida albicans*, comprises a particular class of fungi which are a major medical problem associated with the prolonged use of intravenous solutions and which can be successfully combated by the practice of the present invention. The term "bacteria" is used in its usual context.

By "mycotic infection" herein is meant a disease state within the human or lower animal organism caused by the introduction of fungi, molds or yeasts into the bloodstream by means of an intravenous nutrient solution. Candidiasis is a particular type of mycotic infection which can be prevented, or whose incidence can be substantially lessened, by the practice of this invention.

By "pharmaceutically acceptable" herein is meant materials which are suitable for intravenous administration to humans or lower animals in the amounts specified herein at an acceptable benefit/risk ratio, according to the precepts of sound medical practice.

By "water-soluble" herein is meant soluble at the concentrations disclosed herein, under typical use conditions.

By "antimicrobial agent" herein is meant a material, other than propionic acid or salt thereof, which retards or inhibits the establishment, growth, or proliferation of bacteria, fungi, molds or yeasts in the present compositions. Examples of such agents are described in more detail, hereinafter.

By the term "comprising" herein is meant that various other, compatible, water-soluble ingredients can be present in the compositions of this invention as long as the critical nutrients, pyrogen-free water and antimicrobial agent are present. Typical examples of such materials include electrolytes, pH adjusting agents, sodium chloride, etc., commonly used in intravenous ("i.v.") solutions. The term "comprising" thus encompasses and includes the more restrictive terms "consisting of" and "consisting essentially of" which can be used to characterize the essential materials (nutritive substance, water and antimicrobial agent) used herein.

All percentages herein are by weight, unless otherwise specified.

The preferred antimicrobial agents are the C_4 - C_{12} alkane and C_4 - C_{12} alkene carboxylic acids, as well as sorbic acid, benzoic acid, or any of their water-soluble, pharmaceutically-acceptable salts. Such salts include, for example, the water-soluble sodium, potassium, calcium, and zinc, etc., salts. Also useful herein are combinations of metal salts with the acids, especially with benzoic acid or sorbic acid, as described in the United States Patent 3,404,987 of Looistra and Troller, referred to hereinabove.

As is well known, certain fungi are more susceptible to the action of chemical agents than others. A relatively broad spectrum of fungistatic activity is noted when these acids or their water-soluble salts are employed in the present manner at a concentration in the range of from 0.01% to 10%, especially 0.05 to 10%, of the total compositions. Concentrations of from 2% to 5% of these acids or salts are especially useful for controlling *C. albicans*. It is a matter of routine experimentation to determine antifungal amounts of the organic acids for use in nutritive solutions of the present type to control other phathogenic fungi, yeasts and molds, and conventrations outside the preferred range may be used.

Typical examples of effective fungistats herein include n-butyric acid, n-hexanoic acid, n-octanoic acid and their water-soluble salts; benzoic acid and its water-soluble salts; and sorbic acid (2, 4-hexadienoic acid) and its water-soluble salts. n-Hexanoic acid is especially preferred.

One type of nutritive solution encompassed by this invention comprises a water-soluble sugar as the nutritive substance. Any sugar which can be metabolized and utilized by a human or lower animal as an energy source can be employed in such solutions, but dextrose (i.e., gluclose) is typically used. Listings of

metabolizable sugars appear in standard textbooks.

Dextrose solutions containing antifungal organic acids or their salts can be administered intravenously to humans or lower animals in the treatment of: dehydration; shock; collapse; ketosis of dairy cattle; pregnancy toxemia of sheep; treatment of poisoning by carbon tetrachloride, chloroform and other compounds toxic to the liver; hypoglycemia in piglets, cattle, ewes, dogs; for nutritional purposes; for temporary increases in blood volume; for diabetic coma (together with insulin); for hyperinsulinism; for diuresis in pulmonary edema and increased intracranial pressure; as a sclerosing agent for various veins; and in other standard medical therapies employing dextrose solutions. In general, dextrose is administered intravenously as a 5%-50% solution. Volumes up to several liters, or more, may be administered, as required. Standard reference textbooks describe in detail the concentration of dextrose solution typically administered intravenously in the management of various disease states.

Another type of nutritive solution encompassed by this invention comprises a water-soluble, metabolically-available, nitrogen source as the nutritive substance. In particular, water-soluble amino acid sources, especially sources of the essential amino acids, are used herein. Such materials include, for example, water-soluble acid and base hydrolysates of animal and vegetable proteins; water-soluble polypeptides, either natural or synthetic; and the amino acids, themselves, either in the form of free acids or their water-soluble, pharmaceutically-acceptable salts. The foregoing types of nutritive substances are commercially available and can be modified, in well-known fashion, to improve or adjust their nutritive properties, according to the nutritional requirements of the individual patient.

Nutritive solutions of the foregoing type typically comprise from 0.5% to 30%, preferably from 1% to 20%, of the nitrogen source e.g. an amino acid source.

Another type of nutritive solution encompassed by this invention comprises a lipid (fat) dispersed or dissolved in sterile, pyrogen-free water, e.g. at a concentration of 0.5 to 15%, by weight. Lipid nutrient solutions are commercially available and their use is becoming widespread. However, lipid nutrients are especially susceptible to bacterial/fungal infestation and the practice of this invention is especially important when preparing lipid-based i.v. nutrients.

Another type of nutritive solution encompassed by this invention comprises a mixture of a sugar and a water-soluble, metabolically-available nitrogen source, e.g. an amino acid source, as the mixed nutritive substance. Such solutions comprise a substantially complete dietary replacement for intravenous administration to humans or lower animals in need of such treatment. The sugars and nitrogen sources disclosed hereinabove are used in such solutions.

As can be seen from the foregoing, a number of carboxylic acids can be used to prepare nutritive i.v. solutions and to reduce the incidence of mycotic infection associated with the use thereof. It has now been found that certain of these antimycotic agents also possess excellent antibacterial properties. Since bacterial infestation of i.v. solutions, in use, is becoming recognized as a serious problem in hospitals, the selection of safe, yet effective, agents which reduce the incidence of both fungal and bacterial infestation is important to the field of i.v. therapy.

It has now been discovered that carboxylates such as n-butyric acid, n-hexanoic acid, and n-octanoic acid, especially n-hexanoic acid, exhibit excellent antibacterial and antifungal protection when used in i.v. solutions of the present type. In the case of n-hexanoic acid, bacterial and fungal kill is quite rapid. Moreover, the LD_{50} of hexanoic acid is much higher than any of the other C_2 - C_{12} carboxylic acids when administered i.v. Accordingly, hospital personnel can safely inject a unit dose of n-hexanoic acid into commercial i.v. solutions substantially immediately prior to use and thereby ensure sterility throughout the use situation.

In light of this new discovery of the fast, potent antibacterial/antifungal activity of certain carboxylic acids, the present invention encompasses a process for assuring the sterility of intravenous nutrient solutions and intravenous saline solutions comprising adding to said solutions prior to use (especially immediately prior to use) a safe and effective amount of a C_4 - C_{12} carboxylic acid, or toxicologically-acceptable salt thereof. In a preferred mode, n-hexanoic acid or hexanoate salt is used, inasmuch as the speed-of-kill of the hexanoates is greater than the butyrates and since the hexanoates are somewhat more soluble and metabolically more acceptable than the octanoates. It is to be understood, however, that any of the C_4 - C_{12} carboxylic acids and/or toxicologically-acceptable salts thereof can be used herein, but that the results with the C_6 materials are especially striking and unexpectedly advantageous.

For convenience in use, the carboxylic acids, especially n-hexanoates, can be packaged in unit dosage amounts especially designed for mixing with commercially available i.v. nutrient or saline solutions on site, immediately prior to use. The unit dosage amounts are, of course, based on the volume and concentration of the i.v. solution being treated. For most purposes, i.v. solutions are packaged in one-liter bottles to which is added from about 0.05 ml to about 10 ml of the hexanoate. This is conveniently done by injecting n-hexanoic acid from a sterile ampoule through the rubber septum in the neck

of the i.v. bottle. Thus, in the practice of the present invention, one may employ a sterile ampoule with injection means (e.g., a hypodermic needle) containing a unit dose of a C_4 - C_{12} carboxylic acid or pharmaceutially-acceptable salt thereof, especially n-hexanoic acid or salt thereof.

Preferred sterile solutions for total parenteral nutrition which can easily be prepared on site comprises: from 0.05% to 10% by weight of n-hexanoic acid, or a pharmaceutically-acceptable, water soluble, antibacterial/antifungal salt thereof; from 1% to 20% by weight of a water-soluble amino acid source, especially protein hydrolysates; from 5% to 50% by weight of dextrose; the balance of said solution comprising pyrogen-free water.

As noted, solutions encompassed by this invention can be prepared on site by simply dissolving an effective amount of the antifungal/antibacterial carboxylate in a pre-formed solution of the nutritive substance or substances in pyrogen-free water. In the alternative, the nutrient-carboxylate compositions are prepared and maintained in a closed, sterile container until time of use. Additional sterilization of nutrient solutions comprising carboxylate antimicrobials and sugar can be carried out using heat or filtration techniques well known in the art. Solutions comprising the carboxylate antimicrobials and an amino acid source can likewise be sterilized by heat or filtration. However, when mixtures of sugars and amino acid sources comprise the nutritive substance, it is preferable to avoid heat sterilization, inasmuch as chemical reactions between sugars and amino acids can occur; accordingly, it is preferable to use filtration techniques to sterilize such solutions. Under these latter circumstances, the added protection afforded by the addition of the carboxylate antimicrobial agents herein is substantial and contributes importantly to the safety of such products.

The compositions herein are used according to standard medical techniques for the administration of intravenous solutions. It will be appreciated that the process herein constitutes an improvement in the time-honored method for administering a nutrient solution or dispersion intravenously to humans or lower animals, said improvement comprising admixing with said solution or dispersion a safe and effective amount of a carboxylate antimicrobial agent, especially n-hexanoic acid, or a pharmaceutically-acceptable, water-soluble salt thereof, prior to or concurrently with said administration, whereby a decreased incidence of mycotic and bacterial infection is secured.

Conveniently, the present process is carried out using compositions of the type disclosed hereinabove. Alternatively, the water-soluble fungistatic agent can be packaged and used separately from the nutritive solution and introduced thereto during the course of intravenous feeding. It will also be appreciated that the administration of i.v. nutrients can be carried out by administering the solutions of sugar, amino acids, lipids, saline, etc., separately from each other to help provide the appropriate nutritional balance for the patient. Under such circumstances, the nutrient solutions can contain the antimicrobial carboxylate agent, or the agent can be separately packaged for co-administration through the same apparatus in the manner described above. Accordingly, it will be appreciated that the process herein is not limited to the use of the disclosed compositions, although such use is most convenient. Rather, the antimicrobial agent can be introduced continuously into the intravenous solution during i.v. administration to the patient.

The following examples illustrate the practice of this invention. It will be understood by those skilled in the medical arts that the intravenous solutions prepared in the manner of this invention can be adjusted to a pH in the range of that of the bloodstream by the use of standard acid, base, or buffer materials. In the disclosed compositions, a "safe and effective" amount of the carboxylate antimicrobial agents is used. By "safe and effective" is meant an amount sufficient to inhibit the establishment or growth of microorganisms at a concentration which is non-toxic to the human or animal patient; this, in general, constitutes from 0.01 to 10%, especially 0.05% to 10% by weight of the composition.

EXAMPLE I

A dextrose solution suitable for intravenous administration is prepared by dissolving the following ingredients in pyrogen-free water.

Ingredient	Amt/Liter
Sodium Chloride	2.92 gms
Sodium Acetate	2.722 gms
Potassium Chloride	1.118 gms
Potassium Dihydrogen Phosphate	1.361 gms
Magnesium Chloride	0.355 gms
Calcium Borogluconate	2.40 gms
Anhydrous Dextrose	346.8 gms
n-Hexanoic Acid	10 gms
Trace Mineral Solution*	1 ml

* Zinc chloride 416 mgs, copper sulfate 156 mgs, manganese sulfate 61.3 mgs. sodium iodide 6.6 mgs, in 100 ml of distilled H_2O.

The solution of Example I is cold sterilized by filtration and is suitable for administration to humans and lambs, i.v., for a prolonged period of time with a decreased incidence of mycotic and bacterial infection, even though repeated manipulations of the i.v. apparatus occur.

In the composition of Example I the n-hexanoic acid is replaced by up to about 10 grams of the following acids, respectively: n-butyric; benzoic; and n-octanoic. Excellent results are secured.

EXAMPLE II

The composition of Example I is modified by replacing the hexanoic acid with an equivalent amount of: sodium n-hexanoate; potassium n-hexanoate; sorbic acid; and sodium sorbate, respectively, and excellent results are secured.

EXAMPLE III

A dextrose solution substantially similar to that of Example I is admixed with a nitrogen source comprising a solution of commercial protein hydrolysate (AMINOSOL - modified fibrin hydrolysate, Abbott Laboratories, N. Chicago, I11.) to provide a solution suitable for total parenteral nutrition. A ratio of 3.0 mg. of N_2 per infused Kcal. of dextrose energy input is used.

A solution prepared in the foregoing manner is suitable for the total parenteral nutrition of humans or lower animals for an extended period, by intravenous administration, with a reduced incidence of mycotic and bacterial infection occasioned by such use.

EXAMPLE IV

In the solution of Example III, the n-hexanoic acid is replaced by an equivalent amount of sodium benzoate, sodium n-undecylenate, sorbic acid, n-pentanoic acid, n-butyric acid, n-octanoic acid, and n-nonanoic acid, respectively, to provide solutions useful for i.v. administration to humans or lower animals.

EXAMPLE V

A solution of protein hydrolysate suitable for prolonged intravenous administration to humans or lower animals with a decreased incidence of mycotic infection is as follows:—

Ingredient	Wt.%
Soybean Protein Hydrolysate*	10
Sodium n-Hexanoate	3.5
Sodium Chloride	1.0
Pyrogen-free Water	Balance

*Water-soluble acid hydrolysate, neutralized to pH 7.0 with NaOH.

The solution of Example V is prepared by dissolving the ingredients in the water and is sterilized by heating. The solution is administered, i.v., to a patient at a rate of *ca.* 1 liter per day over a period of several days to provide the patient's nitrogen requirements.

In the composition of Example V, the protein hydrolysate is replaced by an equivalent amount of a mixture comprising nutritionally-adequate amounts of all of the well-known essential amino acids, and equivalent results are secured.

EXAMPLE VI

The total parenteral nutrition of a human or lower animal is carried out as follows.

A sterile dextrose solution is prepared in the manner of Example I, herein, with the deletion of the n-hexanoic acid.

A separately-packaged, sterile solution of protein hydrolysate is prepared in the manner of Example V, herein, with the deletion of the n-hexanoate material.

A separately-packaged, sterile aqueous solution comprising 15% by weight of n-hexanoic acid, adjusted to neutrality with sodium hydrogen phosphate buffer, is prepared.

Individual containers of the three separate sterile solutions prepared in the foregoing manner are assembled on a rack and are directed, downwardly, through three separate sections of sterile tubing to a mixing chamber at the juncture of the tubing. The flow rate of the three individual solutions is adjusted so that they meet in the mixing chamber at a volume ratio of about 1:1:1. The solutions mix on passage through the mixing chamber and are transported therefrom by means of a single tube into the vein of the patient undergoing treatment.

Patients treated in the foregoing manner are less susceptible to mycotic and bacterial infections caused by seepage or spillage of the mixed dextrose and protein hydrolysate solutions at the point of entry into the vein than similar patients fed intravenously in the absence of the n-hexanoic acid.

EXAMPLE VII

A dispersion of fats suitable for intravenous administration is prepared by sonicating purified soybean-derived lipids in sterile, pyrogen-free water. The sonicated lipids remain in a stable *ca.* 10% wt. dispersion by virtue of the trace amounts of natural emulsifiers present in the soybean lipids.

A lipid composition prepared in the foregoing manner is susceptible to infestation by bacteria and fungi. To overcome these problems the sonicated lipid solution is modified by adding 0.1% by weight n-hexanoic acid. The system is buffered to *ca.* pH. 7.0 with mixed sodium phosphate buffers and is ready for use, i.v. The lipid dispersion thus prepared is not only rendered free from contamination by fungi and bacteria, but also is rendered more storage-stable by virtue of the surfactant effect of the hexanoic acid and buffer salts.

Sterile saline solutions (0.1% - 20% NaCl) are prepared from NaCl and pyrogen-free water. Sterility is maintained (at pH 7.0) with 0.2% hexanoic acid.

EXAMPLE VIII

In a convenient mode, the present invention is carried out by injecting the antifungal/antibacterial agents of the present type into commercially-available i.v. nutrient and/or saline solutions prior to use.

Sterile glass syringes, pre-fitted with hypodermic needles, are filled with unit doses (10 ml.) of n-butyric acid, n-hexanoic acid, and n-octanoic acid, respectively. The syringes are packaged under sterile conditions until time-of-use.

One-liter i.v. bottles of commercial dextrose solution, protein hydrolysate, physiological saline and lipid, respectively, are artificially innoculated with strains of streptococcal bac-

teria and/or *C. albicans* to mimic the accidental contamination of i.v. solutions which might occur, undetected, under usage conditions. The unit dosages of the aforesaid acids are injected through the rubber septums of the contaminated i.v. solutions. Excellent antimycotic/antibacterial activity is obtained with the n-butyric acid and n-octanoic acid within a few hours after injection into the contaminated i.v. bottles. With n-hexanoic acid, the same excellent antimycotic/antibacterial activity is obtained within 5-10 minutes.

As can be seen from the foregoing, total parenteral nutrition can now be achieved using compositions which comprise a nutritive amount of lipids, amino acid source, sugar (dextrose), vitamins and minerals dissolved or dispersed in pyrogen-free water and stabilized at physiological pH's with n-hexanoic acid or a toxicologically-acceptable salt thereof.

WHAT WE CLAIM IS:—

1. A method of treating a composition, adapted for intravenous administration and being a saline solution or comprising a nutritive substance and pyrogen-free water, in order to inhibit the growth of microbes therein, which method comprises the inclusion, as an antimicrobial agent, of a water-soluble, pharmaceutically acceptable, C_4 - C_{12} carboxylic acid and/or a water-soluble, pharmaceutically acceptable salt thereof, in an amount such that the concentration of the acid and/or salt thereof is from 0.01 to 10% by weight.

2. A method according to claim 1 wherein the antimicrobial agent is selected from the C_4 - C_{12} alkane and C_4 - C_{12} alkene carboxylic acids, sorbic acid, benzoic acid, and the salts thereof.

3. A method according to claim 2 wherein the antimicrobial agent is selected from n-butyric acid, n-hexanoic acid, n-octanoic acid, and the salts thereof.

4. A method according to claim 1, 2 or 3 wherein the composition comprises as a nutritive substance, a sugar.

5. A method according to claim 4 wherein the sugar is dextrose.

6. A method according to claim 5 in which the composition comprises from 5% to 50% by weight of dextrose.

7. A method according to claim 1, 2 or 3 wherein the composition comprises, as a nutritive substance, an amino acid source (as hereinbefore defined).

8. A method according to claim 7 wherein the amino acid source is a protein hydrolysate.

9. A method according to claim 8 in which the composition comprises from 0.5% to 30% by weight of the protein hydrolysate.

10. A method according to claim 1, 2 or 3 wherein the composition comprises, as a nutritive substance, a mixture of a sugar and an amino acid source (as hereinbefore defined).

11. A method according to claim 10 wherein the sugar is dextrose.

12. A method according to claim 11 in which the composition comprises from 1% to 20% by weight of the amino acid source and from 5% to 50% by weight of dextrose.

13. A method according to claim 10, 11 or 12 wherein the amino acid source is a protein hydrolysate.

14. A method according to claims 1, 2 or 3 wherein the composition comprises, as a nutritive substance, a lipid.

15. A method according to claim 14 in which the composition comprises from 0.5% to 15% by weight of lipid.

16. A method according to any of claims 1 to 15 in which the concentration of the antimicrobial agent is from 0.05% to 10% by weight.

17. A method according to claim 16, in which the concentration of the antimicrobial agent is from 2% to 5% by weight.

18. A method according to claim 1, 2 or 3, in which the composition comprises an amino acid source (as hereinbefore defined), a sugar, a lipid, one or more vitamins and one or more minerals.

19. A method according to claim 1, substantially as described in any one of the Examples.

20. A composition adapted for intravenous administration and comprising a nutritive substance and pyrogen-free water, which composition has been treated by a method according to any of claims 1 to 19.

21. A process for providing parenteral nutrition to a non-human animal, which comprises administering intravenously to said animal a composition according to claim 20.

22. A saline solution which has been treated by a method according to claim 1, 2 or 3.

23. A process according to claim 21, in which the antimicrobial agent is incorporated into the composition concurrently with the intravenous administration.

For the Applicants,
CARPMAELS & RANSFORD,
Chartered Patent Agents,
43 Bloomsbury Square,
London, W.C.1.

Printed for Her Majesty's Stationery Office by MULTIPLEX medway ltd., Maidstone, Kent, ME14 1JS. 1981. Published at the Patent Office, 25 Southampton Buildings, London WC2 1AY, from which copies may be obtained.