Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2580759 C 2013/06/04

(11)(21) 2 580 759

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2005/09/21
(87) Date publication PCT/PCT Publication Date: 2006/03/30
(45) Date de délivrance/Issue Date: 2013/06/04
(85) Entrée phase nationale/National Entry: 2007/03/19
(86) N° demande PCT/PCT Application No.: US 2005/033631
(87) N° publication PCT/PCT Publication No.: 2006/034262
(30) Priorité/Priority: 2004/09/21 (US10/945,810)

(51) Cl.Int./Int.Cl. *A61K 31/66* (2006.01),
A61K 31/185 (2006.01)

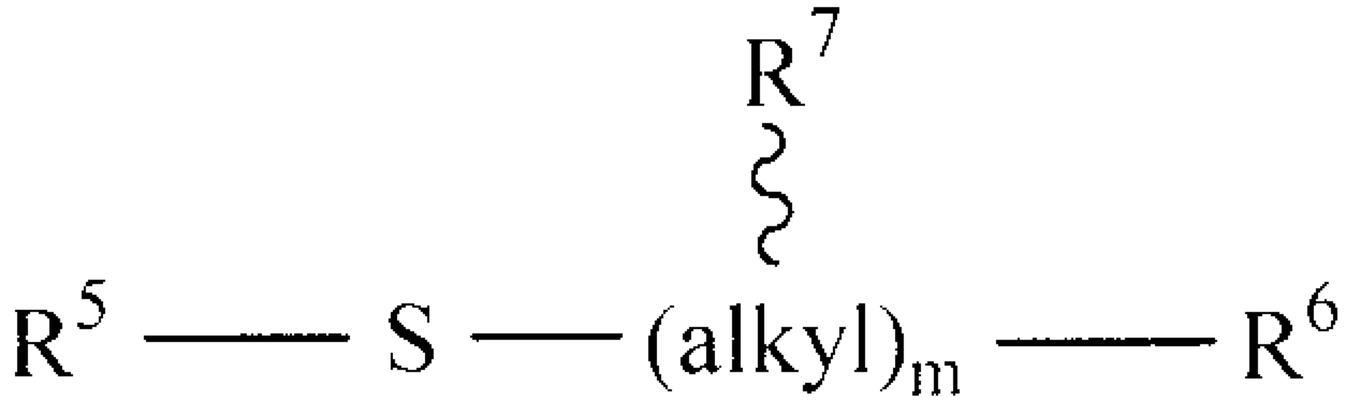
(72) Inventeur/Inventor:
HAUSHEER, FREDERICK H., US

(73) Propriétaire/Owner:
BIONUMERIK PHARMACEUTICALS, INC., US

(74) Agent: MCFADDEN, FINCHAM INC.

(54) Titre : METHODE ET COMPOSITION DE TRAITEMENT DE PATIENTS PAR DIALYSE RENALE
(54) Title: METHOD AND COMPOSITION FOR TREATING PATIENTS UNDERGOING KIDNEY DIALYSIS

(II)



(57) Abrégé/Abstract:
The present invention relates to a method and composition for treating patients who are receiving hemodialysis and/or peritoneal dialysis treatments. The method includes administering to a patient in need of treatment prior to or while undergoing dialysis, an effective amount of a thiol or reducible disulfide compound according to formula (II) as set forth within the Specification. The composition includes a dialysis solution and an effective amount of a thiol or reducible disulfide compound according to formula (II).

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 March 2006 (30.03.2006)

PCT

(10) International Publication Number
WO 2006/034262 A3

(51) International Patent Classification:
A61K 31/66 (2006.01) *A61K 31/185* (2006.01)

(21) International Application Number:
PCT/US2005/033631

(22) International Filing Date:
21 September 2005 (21.09.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/945,810 21 September 2004 (21.09.2004) US

(71) Applicant *(for all designated States except US)*: **BIONUMERIK PHARMACEUTICALS, INC.** [US/US]; 8122 Datapoint Drive, Suite 1250, San Antonio, TX 78229 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **HAUSHEER, Frederick, H.** [US/US]; 203 Kendall Parkway, Fair Oaks Ranch, TX 78015 (US).

(74) Agents: **NADEL, Alan, S.** et al.; Akin, Gump, Strauss, Hauer & Feld, LLP, One Commerce Square, 2005 Market Street, Suite 2200, Philadelphia, PA 19103-7013 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
26 May 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2006/034262 A3

(54) Title: METHOD AND COMPOSITION FOR TREATING PATIENTS UNDERGOING KIDNEY DIALYSIS

$$R^5 - S - (alkyl)_m - R^6 \quad (II)$$
(with R^7 attached to the alkyl group)

(57) Abstract: The present invention relates to a method and composition for treating patients who are receiving hemodialysis and/or peritoneal dialysis treatments. The method includes administering to a patient in need of treatment prior to or while undergoing dialysis, an effective amount of a thiol or reducible disulfide compound according to formula (II) as set forth within the Specification. The composition includes a dialysis solution and an effective amount of a thiol or reducible disulfide compound according to formula (II).

METHOD AND COMPOSITION FOR TREATING PATIENTS UNDERGOING KIDNEY DIALYSIS

FIELD OF THE INVENTION

This invention relates to a method and composition for treating patients undergoing hemodialysis or peritoneal dialysis, commonly referred to as kidney dialysis. The method involves administering an effective amount of a disulfide or thiol-containing compound to the patient prior to or while undergoing the dialysis procedure. The composition includes a dialysis solution and an effective amount of a thiol or reducible disulfide compound.

BACKGROUND OF THE INVENTION

Hemodialysis, hereinafter referred to as kidney dialysis, or simply "dialysis," is a medical procedure that is performed on human patients (and also, on a smaller scale, pet animals), to remove accumulated waste and toxins from the blood in a similar manner to a functioning kidney. When a person or animal's kidneys cease to function properly due to one or more of a number of acute or chronic diseases or conditions (*e.g.*, diabetes, glomerulonephritis and hypertension are commonly recognized medical conditions that are associated with the development of renal failure), toxins accumulate in the bloodstream.

Failure to remove such accumulated waste and toxic compounds - primarily urea, uric acid and its analogues, and other nitrogenous compounds such as creatinine; and excess amounts of elements such as potassium, phosphorous, sodium, chloride and other minerals from the blood results in deterioration of body tissues and organ systems, which eventually results in death if untreated.

Dialysis may be performed in a hospital setting or clinic; or in some cases, the patient is trained to perform the procedure at home on an outpatient basis. Two primary types of dialysis are regularly performed - conventional hemodialysis and peritoneal dialysis. In conventional hemodialysis, the patient is connected (via an arteriovenous fistula, graft or by catheter) to a dialysis machine. The dialysis machine functions to pump the contaminated blood from the patient through a dialyzer, where

the blood is filtered through a dialyzing solution, thereby lowering the concentration of accumulated waste (*e.g.*, urea), and thence returned to the patient. Conventional hemodialysis usually takes between 3-6 hours and is normally performed at a clinic or hospital several times per week. Periodic testing is performed in patients undergoing hemodialysis to assess their medical need to undergo the procedure as well as to monitor the efficacy and timing of hemodialysis treatment.

In peritoneal dialysis, one end of a catheter is inserted into the patient's abdomen, with the catheter connected at its other end to a supply of dialysis solution. In a typical peritoneal dialysis exchange, dialysis solution is introduced into the patient's abdominal cavity through the catheter and allowed to remain there for a predetermined time period (called a "dwell"). During the period when the peritoneal cavity is filled with the solution, waste products and excess body fluids pass through the peritoneum, where they encounter the dialysis solution and are removed from the body when the solution is later drained from the body. The draining/filling process (the "cycle") is normally repeated several times daily, with a long dwell overnight. Periodic testing is performed to monitor the efficacy and timing of performing peritoneal dialysis.

Typical hemodialysis and peritoneal dialysis solutions contain dextrose (glucose), with the solution also including a quantity of salt and other dissolved minerals, and electrolytes as determined by the needs of each patient. The dialysis solution functions to increase osmotic pressure in the peritoneal cavity to cause maximum diffusion of excess fluids and waste products from the blood into the peritoneal cavity. The dialysis solution also serves to bind waste products for removal during the draining process, and to deliver necessary minerals and electrolytes to the body (many renal failure patients are placed on diets that shortchange necessary minerals, and must be ingested separately).

Mesna (sodium 2-mercaptoethene sulfonate) and dimesna (disodium 2,2'-dithiobis ethane sulfonate) are known therapeutic compounds that have heretofore demonstrated a wide variety of therapeutic uses. Both mesna and dimesna have shown protective effects against certain specific types of toxicity associated with the administration of cytotoxic drugs used to treat patients for various types of cancer.

In particular, mesna has been used with some success in mitigating the toxic effects of cytotoxic agents such as ifosfamide, oxazaphosphorine, melphalane, cyclophosphamide, trofosfamide, sulfosfamide, chlorambucil, busulfan, triethylene thiophosphamide, triaziquone, and others, as disclosed in U.S. Patent 4,220,660, issued September 2, 1980.

The improved toxicity profile of dimesna further underscores the usefulness of this compound.

Further, pharmacological profiles of each compound indicate that, if proper conditions are maintained, mesna and dimesna do not prematurely inactivate primary therapeutic drugs to a significant degree.

The molecular structures of both mesna and dimesna are shown below as Structure A and Structure B, respectively.

(A) $HS\text{-}CH_2\text{-}CH_2\text{-}SO_3Na$

(B) $NaSO_3\text{-}CH_2\text{-}CH_2\text{-}S\text{-}S\text{-}CH_2\text{-}CH_2\text{-}SO_3Na$

As shown, dimesna is a dimer of mesna, with the optimum conditions for oxidation occurring in the slightly basic (pH ~7.3), oxygen rich environment found in blood plasma. In mildly acidic, low oxygen conditions, in the presence of a reducing agent such as glutathione reductase, conditions prevalent in the kidneys, the primary constituent is mesna.

Mesna acts as a protective agent for a number of cytotoxic agents by substituting a nontoxic sulfhydryl moiety for a toxic hydroxy (or aquo) moiety. This action is particularly evidenced in the coadministration of mesna and oxazaphosphorine, and in the administration of dimesna along with certain platinum agents and/or taxanes.

Dimesna, as well as some analogues, have favorable toxicity profiles in mammalian species. Dimesna has been administered intravenously to mice and dogs in doses higher than the accepted oral LD50 for common table salt (3,750 mg/kg), with no adverse effects. In Phase I clinical trials, dimensa has been safely administered to humans in doses exceeding 40 g/m^2.

Mesna, and other analogues with free thiol moieties, constitute the more pharmacologically active reductive form of the two types of compounds described in this specification. These compounds manifest their activity by providing highly polar compositions of free thiol moieties for terminal substitution at locations where a terminal leaving group of appropriate configuration, usually a hydroxy, aquo or superoxide is located. Mesna also can form disulfide heteroconjugates with naturally occurring biochemicals that contain a free thiol moiety, such as cysteine, glutathione, homocysteine, and others.

Dimesna and other therapeutic disulfides can be reduced intracellularly by non-enzymatic thiol transfer reactions (SN2) that are mediated by the high intracellular concentration of glutathione and other physiological thiols, thereby generating higher concentrations of intracellular free thiols. The transient production of pharmacologically active free thiols act to scavenge the free radicals and other nucleophilic compounds often responsible for causing cell damage. Dimesna has also been shown to directly scavange free radicals and may confer therapeutic benefit.

This profile is especially significant in explaining the success of dimesna in controlling and mitigating the toxic effects of platinum complex antitumor drugs. The

mechanism for action in the case of cisplatin (*cis*-diammine dichloro platinum) is explained in United States Patent 5,789,000.

Mesna, dimesna, and analogues thereof, are synthesized from commonly available starting materials, using acceptable routes well known in the art. One such method involves the two-step, single pot synthetic process for making dimesna and like compounds of the following formula (I):

(I)

R^1-S-R^2;

wherein:

R^1 is hydrogen, -X-lower alkyl, or -X-lower alkyl-R^3;

R^2 is -lower alkyl-R^4;

R^3 and R^4 are each individually $-SO_3M$ or $-PO_3M_2$;

X is absent or X is sulfur; and

M is an alkali metal.

As used herein, "lower alkyl" means an alkyl group of 1 to 8 carbon atoms.

The process essentially involves a two-step, single pot synthetic process, which results in the conversion of an alkyl sulfonate salt or acid or alkenyl sulfonate salt or acid to the desired formula (I) compound. The process in the case of mesna is a single step process that converts the alkyl or alkenyl sulfonate salt or acid to mesna, or a mesna derivative, by reaction with an alkali metal sulfide or with hydrogen sulfide.

If the desired end product is dimesna or a dimesna analogue, a two-step, single pot process is involved. Step 1 is as described above. Step 2 of the process is performed in the same reaction vessel as Step 1 without the need to purify or isolate the mesna formed during that step. Step 2 includes the introduction of oxygen gas into the vessel, along with an increase in pressure and temperature above ambient values, at least 20 pounds per square inch (psi) and at least 60°C. Dimesna or a derivative thereof is formed in essentially quantitative yield.

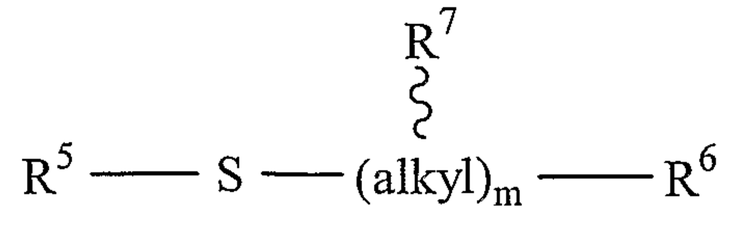
Other processes, well known and documented in the prior art, may be employed to make either mesna or dimesna, or derivatives and analogues thereof.

BRIEF SUMMARY OF THE INVENTION

One aspect of this invention is a method of enhancing therapeutic effects of kidney dialysis in a mammalian patient. It involves the administration of a pharmacologically effective amount of a compound of formula (II), below, to a mammalian patient undergoing or about to undergo hemodialysis or peritoneal dialysis.

The aforementioned compound serves to increase the efficacy of the dialysis detoxification process.

(II)

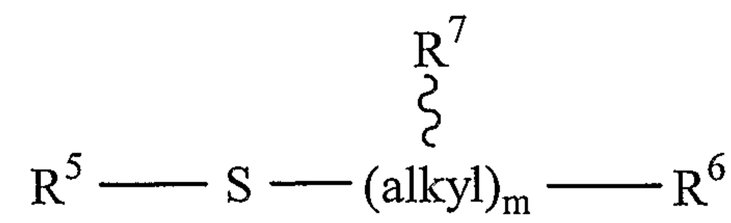


wherein:

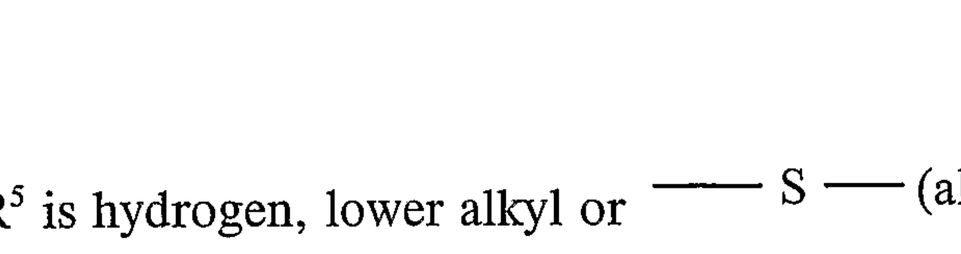
R^5 is hydrogen, lower alkyl or ; R^6 and R^8 are each individually $-SO_3^-M^+$, $-PO_3^{2-}M_2^{2+}$, or $-PO_2S^{2-}M_2^{2+}$; R^7 and R^9 are each individually hydrogen, hydroxy or sulfhydryl; each m is individually 1, 2, 3, 4, 5 or 6, with the proviso that if m is 1, then R^7 is hydrogen; and M is hydrogen or an alkali metal ion; or a pharmaceutically acceptable salt thereof.

Another aspect of this invention is a kidney dialysis composition comprising: a dialysis solution; and a compound of formula (II):

(II)



wherein:



R^5 is hydrogen, lower alkyl or ; R^6 and R^8 are each individually $-SO_3^-M^+$, $-PO_3^{2-}M_2^{2+}$, or $-PO_2S^{2-}M_2^{2+}$; R^7 and R^9 are each individually hydrogen, hydroxy or sulfhydryl; each m is individually 1, 2, 3, 4, 5 or 6, with the proviso that if m is 1, then R^7 is hydrogen; and M is hydrogen or an alkali metal ion; or

a pharmaceutically acceptable salt thereof.

The compound of formula (II), when concomitantly utilized with the processes of hemodialysis or peritoneal dialysis, serves to increase the efficacy of the dialysis to aid in the detoxification of the patient's blood through the removal of various metabolic waste products which may have accumulated to toxic levels within the patient.

Pharmacologically effective amounts of the formula (II) compound to be administered according to the method of the present invention are variable, and are dependent upon the individual patient's needs and/or upon the patient's response. The effective amount will also vary based upon the type of formula (II) compound to be administered, with disulfides usually requiring higher doses than thiols for effective treatment. Also, the type of dialysis procedure (*i.e.*, hemodialysis or peritoneal dialysis) will affect the effective amount of administered formula (II) compound.

However, due to the excellent toxicity profile of the formula (II) compounds, large amounts of the compounds may be administered, such as by continuous IV drip or multiple oral doses, without the risk of untoward side effects commonly associated with other drugs used to treat this condition.

Accordingly, it is an object of this invention to provide for a composition and method of safely and effectively enhancing the efficacy of dialysis treatments.

Another object is to provide a composition and method of enhancing performance of a dialysis procedure by administration of a thiol or reducible disulfide to the patient undergoing or about to undergo dialysis treatment.

Other objects will become apparent upon a reading of the following description.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The preferred embodiments herein described are not intended to be exhaustive or to limit the invention to the precise form disclosed. They are chosen and described to explain the principles of the invention, and its application and practical use to best enable others skilled in the art to follow its teachings.

The method of this invention involves the administration of an effective amount of a formula (II) compound to a patient undergoing or about to undergo kidney dialysis treatment. The effective amount of the formula (II) compound will necessarily depend upon the individual patient's response. Since the formula (II) compounds are essentially nontoxic and cleared rapidly from the patient's body, large amounts of the formula (II) compound can normally be safely administered.

A preferred formula (II) compound is one where:

R^5 is hydrogen, lower alkyl or  ;

R^6 and R^8 are each individually $-SO_3^-M^+$, or $-PO_3^{2-}M_2^{2+}$;

R^7 and R^9 are each individually hydrogen or sulfhydryl;

each m is individually 1-5, with the proviso that if m is 1, then R^7 is hydrogen; and

M is hydrogen or an alkali metal ion; or

a pharmaceutically acceptable salt thereof.

A more preferred formula (II) compound is one where:

R^5 is hydrogen, lower alkyl or  ;

R^6 and R^8 are each individually $-SO_3^-M^+$, or $-PO_3^{2-}M_2^{2+}$;

R^7 and R^9 are each individually hydrogen;

each m is individually 2-4; and

M is hydrogen or an alkali metal ion; or

a pharmaceutically acceptable salt thereof.

Even more preferably, the formula (II) compound is a disulfide, as larger amounts of disulfide compounds may be given safely and effectively when compared to corresponding thiols and thioethers. The most preferred compound is disodium 2,2'-dithiobis ethane sulfonate (dimesna or Tavocept™) administered at a preferred dose of about 0.1 g to about 270 g added to each liter of fluid in the dialysis bag.

Another preferred embodiment of this invention is to administer the formula (II) compound to a patient prior to beginning a hemodialysis treatment. The formula (II) compound is normally administered at a predetermined time prior to beginning of dialysis, preferably 5 minutes to 1 hour prior to the commencement of treatment, most preferably 15 to 30 minutes prior to commencement. In this method of treatment, the formula (II) compound is preferably administered to the patient in an amount of about 1 g/m^2 to about 80 g/m^2 of body surface area of the patient.

Alternatively, the formula (II) compound may be added to the dialysis solution contained in the hemodialysis machine. As previously stated, the even more preferred compounds of formula (II) are the disulfides, and preferred effective amounts of these compounds to be utilized for hemodialysis range from about 0.1 g/L to about 270 g/L. When the formula (II) compound is added to the dialysis solution, the preferred effective amount is defined as a concentration of the formula (II) compound to the solution, ranging from about 0.1 mg/mL to about 270 mg/mL of solution.

For parenteral administration to the patient, the formula (II) compound is dissolved in a suitable solvent, most preferably sterile water that is ideally pyrogen-free, to produce a solution. One or more pharmaceutically acceptable excipients may also be added to provide for an efficacious formulation or to improve handling and administration properties of the solution. The resulting formulation may then be administered by intravenous push, intracavitary or by drip infusion or other accepted medical procedure.

For oral administration the formula (II) compound is preferably combined with one or more pharmaceutically acceptable excipients, fillers and/or diluents. Oral dosage forms may include pills, caplets, tablets, and others. Alternatively, the formula (II) compound may be contained in a deglutable container such as a gelatin capsule or the like, or may be dissolved in water for the patient to drink prior to commencement of dialysis. Additional doses of the formula (II) compound may be repeated if the dialysis treatment lasts more than a few hours.

Careful monitoring and analysis is performed regularly during hemodialysis, with additional doses administered as needed. During peritoneal dialysis, most often performed at home by the patient and an assistant, monitoring may be performed as well to assess the effectiveness of the dialysis, and adjustments made in the treatment as necessary.

The composition according to the present invention includes any typical dialysis solution or one tailored to the needs of a particular patient. A dialysis solution may, by way of example but not of limitation, be comprised of: sterilized pyrogen-free water, dextrose, sodium, potassium, calcium, magnesium, and/or other cations, which may be present as a salt with chloride, acetate, lactate, and/or other anions, and the like. The exact composition of the dialysis solution is ordered by the physician and is dependent upon the patient's specific laboratory values and medical condition. A typical, preferred dialysis solution may be comprised of: dextrose in an amount of approximately 50 g/L, sodium chloride in an amount of approximately 5 g/L, sodium lactate in an amount of approximately 2.5 g/L, calcium chloride in an amount of approximately 1 g/L and magnesium chloride in an amount of approximately 0.5 g/L. The present invention relates to enhancing the performance of the dialysis solution by adding to it a compound of formula (II) in an amount of ranging from 0.1 g/l to 270 g/l.

The following non-limiting, hypothetical example is offered to further explain the invention.

Example 1

Continuous Ambulatory Peritoneal Dialysis (CAPD)

The patient about to undergo CAPD is fitted with an abdominal catheter. The open end of the catheter is connected to a 2 L bag of dialysis solution, which contains

the following dissolved constituents: 100 g of dextrose; 10 g of sodium chloride; 5 g of sodium lactate; 2 g of calcium chloride; 1 g of magnesium chloride; and 40 g of dimesna.

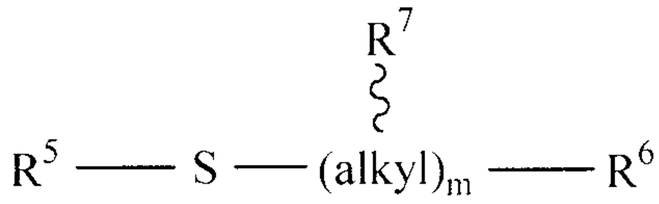
The dialysis solution flows from the bag into the patient's abdomen and the bag is disconnected. The solution is allowed to "dwell" in the patient's abdomen for between 4 to 6 hours, then the catheter is reconnected to the bag and the solution is drained from the abdomen back into the bag. The process is repeated 2 to 4 times daily, and again just prior to the patient's going to sleep at night, whereupon the solution dwells in the abdomen for 6 to 8 hours. Spent dialysis solution may be analyzed from time-to-time in order to determine the efficiency of the dialysis, and to make modifications in treatment, if necessary.

It is understood that the above description is in no way limiting of the invention, which may be modified within the scope of the following claims.

WHAT IS CLAIMED IS:

1. Use of a compound of formula (II):

(II)



wherein:

R^5 is hydrogen, lower alkyl or  ;

R^6 and R^8 are each individually $-SO_3^-M^+$, $-PO_3^{2-}M_2^{2+}$, or $-PO_2S^{2-}M_2^{2+}$;

R^7 and R^9 are each individually hydrogen, hydroxy or sulfhydryl;

each m is individually 1, 2, 3, 4, 5 or 6 with the proviso that if m is 1, then R^7 is hydrogen; and

M is hydrogen or an alkali metal ion; or

a pharmaceutically acceptable salt thereof,

in enhancing therapeutic effects of kidney dialysis in a mammalian patient, wherein a dialysis solution is to be used in the kidney dialysis and the formula (II) compound is a constituent of the dialysis solution.

2. The use according to claim 1, wherein the formula (II) compound is dimesna in an effective concentration in the dialysis solution of about 0.1 g/L to about 270 g/L.

3. The use according to claim 1 or 2, wherein the kidney dialysis is a hemodialysis or peritoneal dialysis procedure.

4. The use according to any one of claims 1-3, wherein the formula (II) compound is dimesna in an effective concentration in the dialysis solution of about 1 g/L to about 200 g/L.

5. The use according to any one of claims 1-4, wherein the compound of formula (II) is a constituent of a continuous ambulatory peritoneal dialysis solution.

6. The use according to any one of claims 1-4, wherein the compound of formula (II) is a constituent of a hemodialysis solution.

7. The use according to any one of claims 1-6, wherein in the formula (II) compound:

R^5 is hydrogen, lower alkyl or $-S-(alkyl)_m-R^8$ (with R^9 on the alkyl);

R^6 and R^8 are each individually $-SO_3^-M^+$, or $-PO_3^{2-}M_2^{2+}$;

R^7 and R^9 are each individually hydrogen or sulfhydryl;

each m is individually 1-5, with the proviso that if m is 1, then R^7 is hydrogen; and

M is hydrogen or an alkali metal ion; or

a pharmaceutically acceptable salt thereof.

8. The use according to any one of claims 1-6, wherein in the formula (II) compound:

R^5 is hydrogen, lower alkyl or $-S-(alkyl)_m-R^8$ (with R^9 on the alkyl);

R^6 and R^8 are each individually $-SO_3^-M^+$, or $-PO_3^{2-}M_2^{2+}$;

R^7 and R^9 are each individually hydrogen;

each m is individually 2-4; and

M is hydrogen or an alkali metal ion; or

a pharmaceutically acceptable salt thereof.

9. The use according to any one of claims 1-8, wherein the formula (II) compound is a disulfide or a pharmaceutically acceptable salt thereof.

10. The use according to any one of claims 1-9, wherein the compound of formula (II) is used in an amount of about 1 g/m^2 to about 80 g/m^2 of body surface area of the patient.

11. The use according to claim 10, wherein the compound of formula (II) is mesna.

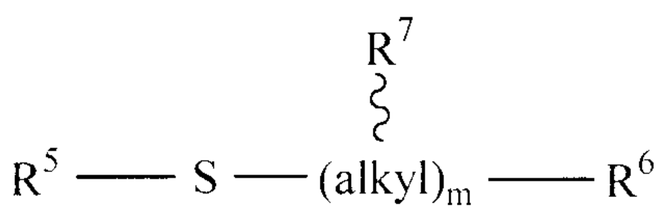
12. The use according to claim 10, wherein the compound of formula (II) is dimesna.

13. A kidney dialysis composition comprising:

a dialysis solution; and

a compound of formula (II):

(II)



wherein:

R^5 is hydrogen, lower alkyl or  ;

R^6 and R^8 are each individually $-SO_3^-M^+$, $-PO_3^{2-}M_2^{2+}$, or $-PO_2S^{2-}M_2^{2+}$;

R^7 and R^9 are each individually hydrogen, hydroxy or sulfhydryl;

each m is individually 1, 2, 3, 4, 5 or 6 with the proviso that if m is 1, then R^7 is hydrogen; and

M is hydrogen or an alkali metal ion; or

a pharmaceutically acceptable salt thereof.

14. The kidney dialysis composition of claim 13, wherein in the formula (II) compound:

R^5 is hydrogen, lower alkyl or  ;

R^6 and R^8 are each individually $-SO_3^-M^+$, or $-PO_3^{2-}M_2^{2+}$;

R^7 and R^9 are each individually hydrogen or sulfhydryl;

each m is individually 1-5, with the proviso that if m is 1, then R^7 is hydrogen; and

M is hydrogen or an alkali metal ion; or

a pharmaceutically acceptable salt thereof.

15. The kidney dialysis composition of claim 13, wherein in the formula (II) compound:

R^5 is hydrogen, lower alkyl or ;

R^6 and R^8 are each individually $-SO_3^-M^+$, or $-PO_3^{2-}M_2^{2+}$;

R^7 and R^9 are each individually hydrogen;

each m is individually 2-4; and

M is hydrogen or an alkali metal ion; or

a pharmaceutically acceptable salt thereof.

16. The kidney dialysis composition of claim 13, wherein the formula (II) compound is mesna.

17. The kidney dialysis composition of claim 13, where the formula (II) compound is dimesna.

(II)