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WO 02/083154 A1

(54) Title: USE OF CATIONIC DEXTRAN DERIVATIVES FOR PROTECTING DOSE-LIMITING ORGANS

(57) Abstract: The present invention discloses the use of cationic dextran derivatives provided with substituents having positively charged side groups as protective agents for dosage limiting organs in systemic treatment of diseases including cancer. The cationic dextran derivatives are particularly useful nephroprotective agents for a subject receiving systemic treatment with cytostatic pharmaceuticals, compounds carrying cytostatic pharmaceuticals, radionuclides or compounds carrying radionuclides against renal damage. The cationic dextran derivatives not only protect the dose-limiting organs but are better tolerated and have less side effects than conventionally used protective agents.

USE OF CATIONIC DEXTRAN DERIVATIVES FOR PROTECTING DOSE-LIMITING ORGANS

The Field of the Invention

The present invention is related to the use of cationic dextran derivatives for protecting dose-limiting organs especially kidneys during systemic treatment of cancer or other diseases. Also disclosed is a method for protecting dose-limiting organs in patients subjected to systemic therapy by administrating cationic dextran derivatives. The cationic dextran derivatives not only protect the dose-limiting organs, but are better tolerated and have less side effects than conventionally used protective agents.

The Background of the Invention

Systemic therapy refers to the intravenous infusion of therapeutic drugs. Drugs in this context can be cytostatic pharmaceuticals, compounds carrying cytostatic pharmaceuticals, antibiotics, radionuclides or compounds carrying radionuclides. These drugs, including other therapeutically active chemicals are known to have substantial side effects on certain vital organs including kidneys. The intensity of the systemic treatment, i.e. the infused dose and its frequency, is limited by said dose-limiting organs. Two important dose-limiting organs are kidneys and bone marrow. This means that for each drug or drug combination there is a maximum dose that these organs can tolerate. Above this dose maximum the organs are seriously and permanently damaged by side effects caused by the drug. This restricts the drug dose that can be used and the frequency of its administration. If the dose can be increased without damaging the organs, the probability of successful treatment increases.

Currently, there are few drugs available for protecting dose-limiting organs during systemic therapy. Some protective agents are described in the patent US 5,290,538, which discloses the use of nephroprotective infusion solutions containing soluble L-amino acids, which are administered intravenously to patients to protect their kidneys from nephrotoxic agents. The patent application DE 34 14 491 discloses a mixture of L-amino acids, which is developed for this purpose. However, said amino acid mixtures may have detrimental effects on the kidney, by inducing acute renal failure or potentiating a preexisting acute renal failure. The commonly known amino acid mixtures are not suitable for kidney protection against the toxic effects of cytostatic and immunosuppressive agents. The patent publications US 5,087,441, US 5,010,092 and EP 0 434 470 disclose the use of methimazole or carbimazole for reducing nephrotoxicity due to antibiotics, radiological

contrast media, metal or metal compounds as well as environmental toxins. To achieve the desired kidney protection, large amounts i.e. gram quantities of kidney protective agents are required. Such large doses are known to be connected with pronounced and sometimes serious side effects, e.g. nausea and vomiting, including grade I and II gastrointestinal toxicity, and sometimes disturbance of electrolyte balance affecting heart function. Consequently, there is a need for new methods and more effective agents with less side effects for protecting dose-limiting organs, including kidneys. The objective of the present invention is to provide novel alternative agents having significant less side effects for manufacturing medicines effectively protecting dose-limiting organs, especially kidneys.

The Summary of the Invention

The objectives of the present invention are achieved by employing cationic dextran derivatives that is dextran substituted with positively charged substitutents, particularly amino acid residues from a group consisting of lysine, arginine, histidine, ornithine and mixtures thereof.

The present invention provides the use of such cationic dextran derivatives for manufacturing medical compositions, including infusion solutions and injectable formulations for the protection of dose-limiting organs particularly kidneys during systemic therapy in treatment of cancer as well as other diseases. The cationic dextran derivatives not only protect the dose-limiting organs, but are better tolerated and have minimal side effects compared to conventional protective agents.

The present invention provides cationic dextran derivatives for manufacturing medical compositions for protecting dose-limiting organs, such as kidneys and bone marrow during systemic therapy of certain diseases, particularly cancer. The cationic dextran derivatives comprise dextran the sugar monomers of which are substituted with substituents having positively charged cationic side groups, preferably amino groups. The dextran moiety has a molecular weight of 50 kDa or less, preferably a molecular weight between 10-50 kD, more preferably 20-40 kD. The positively charged cationic side groups are selected from a group consisting of the positively charged amino acids such as lysine, arginine, histidine, ornithine and mixtures thereof. A particularly useful substituent is lysine. A substantially sufficient substitution degree is 0.05 - 25 mol cationic residues / mol dextran, preferably 0.5 - 20 mol cationic residues / mol dextran, most preferably 5 - 10 mol cationic residues / mol dextran. 10-25 mol cationic substituents / mol dextran being a particularly suitable range.

The present invention provides a method for protecting a subject from damages in dose-limiting organs caused by effects of radioactive or cytotoxic agents during systemic treatment. The method comprises the administration of an effective amount of a cationic dextran derivative that is dextran provided with substituents having positively charged cationic side groups, to a subject in association with or before the administration of a chemotherapeutic, radioactive or immunosuppressive agent. The present invention particularly provides a method of protecting a subject from renal damage caused by nephrotoxic effects of radioactive or cytotoxic agents during systemic treatment of cancer. Said method comprises the administration of a kidney protecting amount of a cationic dextran derivative provided with a substituent having positively charged cationic side groups to the subject in association with or before the administration of a chemotherapeutic, radioactive or immunosuppressive agent. In the method of the present invention the cationic dextran derivative is provided in an intravenously administrable dosage form or they are intravenously co-administrated or co-infused with the drugs used in the systemic therapy.

Brief description of the drawings

Figure 1A depicts whole body images showing the anterior (front) and exterior (back) of a patient 3 hours after infusion without renal protection.

Figure 1B depicts whole body images showing the anterior (front) and exterior (back) of a patient 3 hours after infusion with renal protection.

Figure 2A depicts blood clearance and kidney uptake as demonstrated by a curve indicating the percentage injected activity in blood as a function of time in the same patient without renal protection (basal), with prior art protection (amino acid) and with lysine substituted dextran (dextran+Lysine).

Figure 2B depicts blood clearance and kidney uptake as demonstrated by a curve indicating the percentage injected activity in kidneys as a function of time in the same patient without renal protection (basal), with prior art protection (amino acid) and with lysine substituted dextran (dextran+Lysine).

The Detailed Description of the Invention

Definitions

In the present invention the terms used have the meaning they generally have in the fields

of biochemistry, radiology, physiology and pharmacology, but some terms are used with a somewhat deviating or broader meaning than in the normal context. Accordingly, in order to avoid uncertainty caused by terms with unclear meaning some of the terms used in the specification and in the claims are defined in more detail below.

The term "**systemic therapy**" means the medication including cytostatic agents, radioactive substances and/or immunosuppressants pertaining to or affecting the body as a whole e.g. via blood circulatory system. Systemic therapy in cancer treatment refers to the intravenous infusion of therapeutic drugs. Drugs in this context can be cytostatic pharmaceuticals, compounds carrying cytostatic pharmaceuticals, radionuclides or compounds carrying radionuclides. The intensity of the systemic treatment, i.e. the infused dose and its frequency, is limited by so called dose-limiting organs.

The term "**dose-limiting organs**" refers to those organs e.g. the kidneys and bone marrow that are seriously and permanently damaged when a systemically administered drug is administered above a certain dose. This means that for each drug or drug combination there is a maximum dose that these organs can tolerate. This dose limits the efficacy of the drug, since a higher dose, which would be useful for treating the cancer or other disease is detrimental and not be used because it has toxic side effects on the sensitive organs.

The term "**protection of dose-limiting organs**" or specifically "kidney (nephro) protection" means the protection of the sensitive organ, specifically protection against renal damage in a patient receiving systemic cancer therapy with potentially nephrotoxic drugs. In the present invention the protection is achieved by infusion of cationic dextran derivatives which provides the negatively charged kidney with a layer, which allows a smooth and rapid passage of the drug preventing uptake in kidneys, thus preventing nephrotoxicity.

The term "**dextran**" is applied to polysaccharides, i.e. high-molecular-weight polymers of D-glucose, produced by glycosyltransferase on the cell surface of certain lactic acid bacteria growing on a sucrose substrate. Several organisms produce dextrans, but only *Leuconostoc mesentroides* and *L. dextranicum* have been used commercially. The chemical and physical properties of the dextrans vary with the method of production. Native dextrans usually have a high molecular weight; lower molecular weight clinical dextrans are usually prepared by depolymerization and subsequent fractionation of the native dextrans.

The dextrans used for kidney protection preferably have a molecular weight, which is

below the kidney filtration threshold for clinical dextrans, i.e. 50 kD or less. Dextrans with a molecular weight above 50 kD are not filtrated through the kidneys. The molecular weight of the invention preferably varies between 10-50 kD. The average molecular weight being 40 kD. This means that the cationic dextran derivatives for kidney protection comprises on average 222 glucose monomers, the mean range being ±50 glucose monomers.

In the present invention the term "**cationic dextran derivatives**" means dextrans having the structure, properties and functions defined above for "**dextrans**", but which dextrans are substituted with positively charged side groups, such as amino groups, preferably amino acid residues. The positively charged groups, which preferably are amino acid residues, are selected from a group of amino acids including lysine, arginine, histidine, ornithine an mixtures thereof, but also other positively charged substituents can be used. Diaminated alkyl chains are examples of other such substituents.

The degree of substitution should be such that the positive charge of the cationic dextran derivatives is sufficiently high to be attracted by the negatively charged kidney, but not so high that it is permanently attached to the kidney and cannot be removed from the kidney. A sufficient substitution degree is 0.05 - 25 mol substituents / mol dextran, more preferably 0.5 - 20 mol substituents / mol dextran, most preferably 5 - 10 mol substituents / mol dextran. An optimal substitution degree is obtained when 10 - 25 mol substituents / mol dextran are coupled.

In addition to the positively charged substituents, which preferably are the amino acid residues listed above, the cationic dextran derivatives of the present invention can be chemically substituted forming dextran derivatives including for example, alkylated, esterified, etherified or amidized forms with a low substitution degree. Especially advantageous are small molecule substituents having aminated methyl or ethyl groups as substituents. The substitution should not disturb the protective properties and functions of the cationic dextran derivatives.

The General Description of the Invention

When studying patients with somatostatin receptor positive tumors and investigating the renal protective efficacy of different agents, it was surprisingly observed that a cationic dextran polymer to which lysine was covalently linked, showed a high kidney protection capacity and had no side effects.

Based on this preliminary observation, it was deducted that dextrans substituted with cationic side groups, preferably amino acids carrying positively charged side groups, particularly lysine-dextran conjugates can be used to protect kidneys when administering potentially nephrotoxic drugs. It was demonstrated that the dosage of the drug could be increased by 25-30% because of the effective inhibition of the nephrotoxicity. This means that a significantly higher dose of the drug could be used. In fact, said increased dosage of drug may provide the additional efficacy necessary for curative treatment of the disease e.g. cancer.

Accordingly, the present invention is based on studies, in which it has been demonstrated for the first time that infused dextrans, substituted with lysine or another positively charged side group, including amino acid residues such as arginine, histidine, ornithine and mixtures, covalently linked to the dextran via an amine bond, protect the kidneys during systemic therapy more effectively than commonly used nephroprotective agents, such as amino acid mixtures and positively charged proteins. Additionally, the cationic dextran derivatives show no significant side effects.

The substituted cationic dextran derivative of the present invention comprises dextrans or dextran derivatives substituted with residues having positively charged side groups, preferably amino acids, which are covalently coupled to the activated hydroxyl groups of the glucose monomers in the dextran chains either by ether, ester or amine bonds.

The substituted cationic dextran derivatives, substituted with aminated alkyl groups, lysine, histidine, arginine, ornithine or mixtures thereof, are cationic polymers having an overall positive effective charge, whereas kidney is charged negatively leading to an effective blocking of the toxic effects of the drugs.

The nephroprotective effect is believed to be obtained by the fact that the positively charged cationic dextran derivatives of the present invention are attracted (attached) to the negatively charged tissues of kidney and other dose-limiting organs and thereby allow the cytotoxic and radioactive agents as well as immunosuppressives to pass the kidneys thus preventing uptake of the drug through the proximal tubuli of the kidneys. By preventing the uptake by the kidneys of radioactive and/or cytotoxic drugs, higher doses can be used thus increasing treatment efficacy.

Since the cationic dextran derivatives are macromolecules they seem to block the uptake of drugs more effectively than monomers, such as conventionally used amino acids or amino acid mixtures used as such. The positively charged macromolecule, preferably the cationic

dextran derivatives blocks the negative charges of the proximal tubules tissue more effectively than amino acids *per se*. Also the time a macromolecule blocks the drug uptake in kidneys is longer than that of a monomer. Since a smaller amount can be used due to the good binding capacity of the dextran derivatives less, if any side effects occur.

Intravenous administration of the cationic dextran derivatives of the present invention to patients subject to cytostatic treatment counteracts toxic renal damage resulting from cytostatic drugs or that resulting from immunosuppressive agents.

The dose of the cationic dextran derivatives of the present invention as well as the time of administration is optimized in such a way that the accumulation kinetics in the tumor and the elimination of the drug produces an optimal radiation dose relation between the tumor and the rest of the organism.

The use of the present invention is preferably aimed at renally healthy patients who are at risk of being subjected to renal damage due to systemic treatment of another ailment with cytostatic pharmaceuticals, compounds carrying cytostatic pharmaceuticals, radionuclides or compounds carrying radionuclides. The composition is specifically directed to block toxic effect of said cytostatic pharmaceutical compounds used in systemic therapy.

It is generally known that the charge of the polydisperse macromolecule is highly affected by the media in which the macromolecule of interest is situated. Said media dependent so called effective surface charge can deviate remarkably from the theoretical electric charge of the molecule based on the amount of dissociated groups. Said deviation is especially remarkable in a physiological medium, for example, in a human being, injected with said drug.

The evaluation of the effective surface charge is carried out with a multitude of different test systems, e.g. measuring of zeta-potentials. According to the generally accepted opinion, methods based on electrophoresis give the values, which best describe the actual situation. The effective surface charge can be determined exactly with test system based on convective electrophoresis.

Synthetic methods described in the dissertations of Anders Holmberg, Dextran Conjugates for Tumour Targeting, Synthesis and Characterisation, Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 546, ACTA Universitatis Upsaliensis, Uppsala, Sweden, 1995 and Jin Du, Derivatives of Dextran Synthesis and Application in Oncology, Academic Dissertation from the Faculty of Mathematics and Natural Sciences

of the University of Jyväskylä, Jyväskylä, Finland (2001) can be used for preparing the cationic dextran derivatives of the present invention.

The cationic dextran derivatives of the present invention can be purified with conventional methods including chromatography and ultrafiltration.

The cationic dextran derivatives of the present invention comprise less than 20 % (w/w), preferably 5-15 % (w/w), more preferably 15-20 % (w/w), most preferably 20 % (w/w) of substituents or residues, preferably amino acid residues.

Preferably, the charged substituents or residues are bound to 15-30 % of the glucose monomers of said dextran.

The compounds according to the invention in the basic form or in combination with pharmaceutically acceptable additives, carriers, adjuvants, etc. are valuable protective agents for dose-limiting organs and particularly valuable nephroprotective agents.

The cationic dextran derivatives of the present invention can be provided in free form or as salts. Salts include salts formed from acid, e.g. organic acids, polymeric acids or inorganic acids, of which hydrochlorides and acetates are examples and forms of salts, which are formed from carboxylic groups or sulfonic acids.

The kidney protective efficacy of the cationic dextran derivatives of the present invention can be demonstrated in patients with somatostatin receptor positive tumors. The systemic therapy can be carried out by administering the cationic dextrans of the present invention before or simultaneously with the radioactive drug intravenously or by other suitable means of administration. Kidney dose reduction after infusion of the protective agents can be evaluated by different means, including Medical Internal Radiation Dose (MIRD) formalism, followed by intrapatient analysis.

The invention is demonstrated by the following example, which is provided for illustrative purposes and should not be used to limit the scope of invention.

Example 1

Renal protective effects of dextran-lysine (DxL), arginine-lysine (LAL) mixture and a standard cationic protein used in hospitals

Fifteen patients (5 patients/group) with somatostatin receptor positive tumors, which are

characterized by high-density somatostatin receptors, were studied to investigate the renal protective efficacy of three different agents i.e. dextran-lysine (DxL), arginine-lysine mixture (LA) and a positively charged protein, i.e. avidine (caP), which is used as a standard at Instituto Europeo di Oncologia, Divisione di Midicina Nucleare, Milano, Italia. Each patient underwent two dosimetric evaluations within two weeks, the first without protective agent and the second with infusion of protective agent (DxL 2 mg/kg, LA 400 mg/kg and caP 2 mg/kg). In both cases 185 Mbq ^{111}Indotatoc was administered intravenously (i.v). Whole body images were acquired at 30 min, 3, 16, 24 and 48 h post injection. Pharmacokinetics was determined by collecting blood and urine samples up to 50 h post injection. Kidney dose reduction after infusion of the protective agents was evaluated by Medical Internal Radiation Dose (MIRD) formalism with an intrapatient analysis.

The mean kidney absorbed dose was reduced ca. $31\pm25\%$ with the conventional lysine-arginine (LA) mixture, ca. $50\pm13\%$ with the positively charged protein (caP) more than $50\pm24\%$ with dextran-lysine compound (DxL). No relevant differences were found in blood clearance with or without Cationic-Dextran. Urinary excretion curves were similar, except for a slight faster (10%) rate within the first few hours after injection with a cationic dextran derivative (DxL). Apart from kidney uptake, the biodistribution in other organs was not significantly modified. Time-activity curves for kidneys showed the same trend with and without protection, but with a lower uptake as demonstrated by percentage injected activity (%IA) at all time points.

Side effects occurred with LA and caP i.e. grade I-II gastrointestinal toxicity. No side effects were observed with dxL. In conclusion, dextran-lysine shows high kidney protection capacity without side effects.

The results are also shown in Figures 1A-1B and 2A-2B. In Figure 1 whole body images in anterior (from the front) and posterior (from the back) views of the same patient 3 h after injection are shown. 1A shows images without renal protection and 1B shows images with renal protection using dextran-lysine (DxL). Figure 1B shows reduced doses of kidney absorption and higher activities in the bladder. In Figure 2 blood clearance and kidney uptake without renal protection (basal), with amino acids protection and with DxL protection are shown for the same patient.

Claims

1. Use of a cationic dextran derivative for manufacturing a medical compositions for protecting dose-limiting organs during systemic therapy of diseases.

2. The use according to claim 1, **characterized** in that the sugar monomers of dextran are substituted with substituents having positively charged cationic side groups, preferably an amino group.

3. The use according to claims 1-2, **characterized** in that the dextran has a molecular weight of 50 kDa or less, preferably a molecular weight between 10-50 kD, more preferably 20-40 kD.

4. The use according to claims 1-3, **characterized** in that the substituents having positively charged cationic side groups are selected from a group consisting of the positively charged amino acids, lysine, arginine, histidine, ornithine and mixtures thereof.

5. The use according to claims 1-4, **characterized** in that the substituent is lysine.

6. The use according to claims 1-5, **characterized** in that a substantially sufficient substitution degree is 0.05 - 25 mol cationic residues / mol dextran, preferably 0.5 - 20 mol cationic residues / mol dextran, most preferably 5 - 10 mol cationic residues / mol dextran.

7. The use according to claims 1-6, **characterized** in that the substitution degree being 10-25 mol cationic substituents / mol dextran.

8. The use according to claims 1-7, **characterized** in that the dose-limiting organ comprises kidney.

9. The use to claims 1-8, **characterized** in that the systemic therapy comprises cancer treatment.

10. A method of protecting a subject from damage in dose-limiting organs caused by effects of radioactive or cytotoxic agents during systemic treatment, said method comprising the administration of an effective amount of a cationic dextran derivative provided with substituents having positively charged cationic side groups, to a subject in association with or before the administration of a chemotherapeutic, radioactive or

immunosuppressive agent.

11. The method according to claim 10, wherein the sugar monomers of dextran are substituted with substituents having positively charged cationic side groups.

12. The method according to claim 11, wherein the cationic side groups are amino groups.

13. The method according to claim 10, wherein the dextran has a molecular weight of 50 kDa or less.

14. The method according to claim 10, wherein the substituent having a cationic side group is an amino acid selected from a group consisting of lysine, arginine, histidine, ornithine and mixtures or thereof.

15. The method according to claim 10, wherein that the substituent is lysine.

16. The method according to claim 10, wherein the substitution degree of the cationic dextran derivative is 0.05-25 mol substituents / mol dextran, preferably 0.5-20 mol substituents / mol dextran, most preferably 5 - 10 mol substituents / mol dextran.

17. The method according to claim 10, wherein the substitution degree of the cationic dextran derivative is 10-25 mol substituents / mol dextran.

18. The method according to claim 10, wherein the cationic dextran derivative is provided in an intravenously administrable dosage form.

19. The method according to claim 10, wherein the cationic dextran derivative is intravenously co-administrated or co-infused with the drugs used in the systemic therapy.

20. A method of protecting a subject from renal damage caused by nephrotoxic effects of radioactive or cytotoxic agents during systemic treatment of cancer, said method comprising the administration of a kidney protecting amount of a cationic dextran derivative provided with a substituent having positively charged cationic side groups, to a subject in association with or before the administration of a chemotherapeutic, radioactive or immunosuppressive agent.

21. The method according to claim 20, wherein the sugar monomers of dextran are substituted with substituents having positively charged cationic side groups.

22. The method according to claim 21, wherein the cationic side groups are amino groups.

23. The method according to claim 20, wherein the dextran has a molecular weight of 50 kDa or less.

24. The method according to claim 20, wherein the substituent having a cationic side group is an amino acid selected from a group consisting of lysine, arginine, histidine, ornithine and mixtures thereof.

25. The method according to claim 20, wherein that the substituent is lysine.

26. The method according to claim 20, wherein the substitution degree of the cationic dextran derivative is 0.05-25 mol substituents / mol dextran, preferably 0.5-20 mol substituents / mol dextran, most preferably 5 - 10 mol substituents / mol dextran.

27. The method according to claim 20, wherein the substitution degree of the cationic dextran derivative is 10-25 mol substituents / mol dextran.

28. The method according to claim 20, wherein the cationic dextran derivative is provided in an intravenously administrable dosage form.

29. The method according to claim 20, wherein the cationic dextran derivative is intravenously co-administrated or co-infused with the drugs used in the systemic therapy.

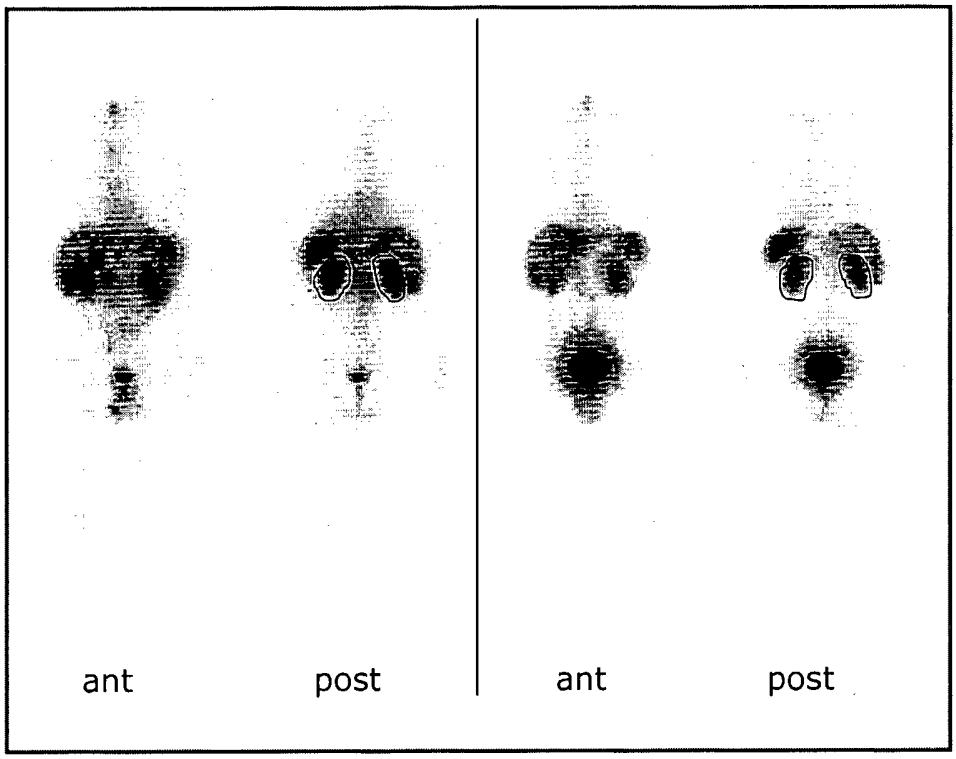
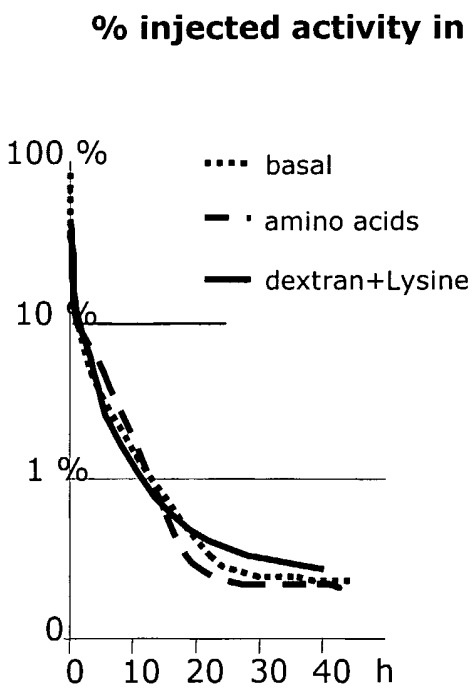


Fig 1A

Fig 1B

Fig 2A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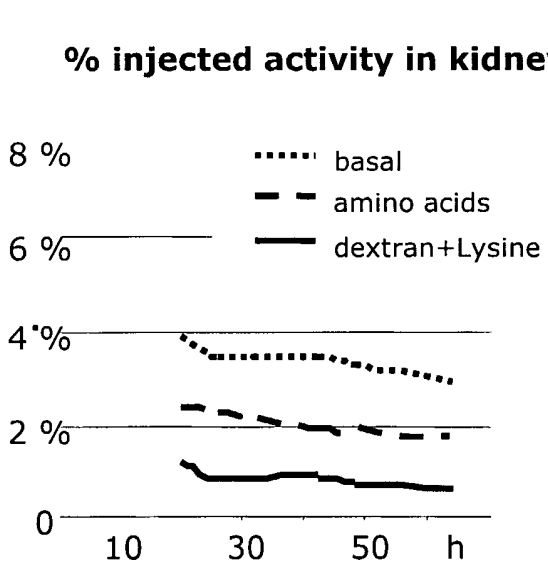
100 %
10 %
1 %
0
basal
amino acids
dextran+Lysine
0 10 20 30 40 h

Fig 2B


% injected activity in kidneys
8 %
6 %
4 %
2 %
0
basal
amino acids
dextran+Lysine
10 30 50 h

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 02/00305

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/721, C08B 37/02
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61L, C08B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 0021571 A1 (MAP AB), 20 April 2000 (20.04.00) --	1-9
A	US 5290538 A (HAGEN BERTEMANN), 1 March 1994 (01.03.94) --	1-29
A	WO 0105383 A2 (MALLINCKRODT, INC.), 25 January 2001 (25.01.01) --	1-29
A	DE 3414491 A1 (DIETL, HANS, DR.), 24 October 1985 (24.10.85) -- --------	1-29

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search	Date of mailing of the international search report
16 August 2002	23 -08- 2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Erika Stenroos/Els Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

06/07/02

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WO 0021571 A1	20/04/00	AU 1424700 A	01/05/00
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