OPIC
Office de la propriété intellectuelle du Canada

CIPO
Canadian Intellectual Property Office

(12) (19) (CA) **Brevet-Patent**

(11) (21) (C) **2,027,743**
(22) 1990/10/16
(43) 1991/05/16
(45) 2000/03/21

(72) Ueno, Ryuji, JP
(73) Kabushikikaisha Ueno Seiyaku Oyo Kenkyujo, JP

(51) Int.Cl.[5] A61K 31/715
(30) 1989/11/15 (298091/1989) JP

(54) **DIURESE AU MOYEN DES CYCLODEXTRINES ET DE LEURS DERIVES**

(54) **DIURESIS BY CYCLODEXTRINS AND THEIR DERIVATIVES**

(57) The present invention is directed to a pharmaceutical composition for diuresis improvement comprising a cyclodextrin or a derivative thereof in association with a pharmaceutically acceptable carrier, diluent or excipient.

2027743

ABSTRACT

The present invention is directed to a pharmaceutical composition for diuresis improvement comprising a cyclodextrin or a derivative thereof in association with a pharmaceutically acceptable carrier, diluent or excipient.

2027743

IMPROVEMENT IN DIURESIS BY CYCLODEXTRINS AND THEIR DERIVATIVES

The present invention relates to a pharmaceutical composition for diuresis improvement comprising a cyclodextrin or a derivative thereof.

Such improvement is required in subjects who show anuria or oliguria.

Anuria refers to a state wherein daily micturination is less than 100 ml and oliguria refers to a state

wherein daily micturination is between 100 and 400 ml. Anuria and oliguria include those of prerenal, renal and prostrenal nature.

Prerenal anuria is caused by a decrease in the renal bloodstream and originates from cardiac insufficiency, cirrhosis, dehydration, shock, etc. Renal oliguria is caused by different renal diseases. Acute nephritis and nephrotic syndrome are due to reduced glomerular filtration and enhanced tubular resorption of sodium ion and water. Acute renal insufficiency (acute tubulorrhexis) is principally caused by reduced glomerular filtration.

Since anuria and oliguria destroy the equilibrium in the body fluid and may lead to edema, uremia, cardiac insufficiency, hypertensive encephalopathy, retinitis etc., treatment of them is required.

Moreover, even in the case where the amount of urine is normal, diuretics are often used in the treatment of cardiovascular diseases or renal diseases, e.g. hypertension, edema, etc.

As a result of extensive study concerning the properties of cyclodextrins and their derivatives which have been used only as a complexing agent in the pharmaceutical field, the present inventor discovered that these compounds exhibit a beneficial diuretic action.

In a first aspect, the present invention provides a method for diuresis improvement which comprises administering, to a subject in need of such improvement, a cyclodextrin or a derivative thereof (hereinafter, referred to as the compound used in the invention) in an amount effective to cause such improvement.

In a second aspect, the present invention provides for the use of a cyclodextrin or a derivative thereof for the manufacture of a medicament for diuresis improvement.

In a third aspect, the present invention provides a pharmaceutical composition for diuresis improvement comprising a cyclodextrin or a derivative thereof in association with a pharmaceutically acceptable carrier, diluent or excipient.

As used herein, the term "diuresis" refers to increased extracorporeal excretion of water, electrolytes, final metabolites, etc. Usually, such excretion results in an increase in the amount of urine. The compounds used in the invention exhibit an action of increasing water secretion and secreting electrolytes. Increase in creatinine clearance (glomerular filtration) has also been comfirmed indicating that the compounds used in the invention also exhibit an action of increasing renal blood stream and glomerular filtration. The compounds of the invention

have been indicated in the treatment of renal hypofunction anuria, oliguria, hypertension of various etiologies, edema derived from various causes, promotion of drug excretion when drug intoxication has occurred, adjustment of the pressure and amount of aqueous humor or cerebrospinal fluid, etc. Also, the compounds used in the invention have been indicated in the treatment of renal insufficiency by e.g. acute tubulorrhexis, necrosis of renal cortex, etc. and nephritis.

The term "treatment" includes prevention, cure and relief of disease and arrest or relief of the development of disease.

The term "cyclodextrin" includes α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin.

The term "derivatives" used in conjunction with the term cyclodextrin refers to compounds in which at least one atom selected from hydrogen, oxygen or carbon in the cyclodextrin molecule is replaced by an atom or a group of atoms ordinarily present as a substituent in this type of organic compound (saccharides). These derivatives include etherified cyclodextrins, branched cyclodextrins, acylated cyclodextrins and sulfur-containing cyclodextrins.

Said etherified cyclodextrins include (lower)-alkylcyclodextrins, e.g. methylcyclodextrin, ethylcyclodextrin, propylcyclodextrin, dimethylcyclodextrin, trimethylcyclodextrin etc., (lower)alkenylcyclodextrins,

hydroxy(lower)alkylcyclodextrins, e.g. hydroxyethylcyclodextrin, hydroxypropylcyclodextrin, etc., (lower)alkoxy(lower)alkylcyclodextrins, aralkylcyclodextrins, e.g. benzylcyclodextrin, etc., halo(lower)alkylcyclodextrins, e.g. chloroethylcyclodextrin, etc., and cylodextrin-epichlorohydrin copolymer and so on. These may be etherified cyclodextrins in which one, two or three hydroxy groups in any of the glucose units of the cyclodextrin molecule are converted into ether.

Said branched cyclodextrins include glucosylcyclodextrin, maltosylcyclodextrin, etc.

Said acylated cyclodextrins include (lower)alkanoylcyclodextrins, e.g. formylcyclodextrin, acetylcyclodextrin, etc., aromatically or heterocyclically acylated cyclodextrins, e.g. benzoylcyclodextrin, nicotinoylcyclodextrin, etc.

Said sulfur-containing cyclodextrins include sulfonated cyclodextrins, etc.

The derivatives of cyclodextrin also include derivatives in which two or more derivatizations selected from etherification, branching, acylation and sulfuration co-exist.

These derivatives are known or can be prepared by a method similar to that for the known derivatives.

While the dosage of cyclodextrin or derivatives

thereof will vary depending on age, weight, condition of the particular subject, desired therapeutic effect etc., satisfactory effects will generally be obtained with a dosage of 1 μg/kg to 500 mg/kg, preferably 10 μg/kg to 50 mg/kg, administered once a day or in 2 to 4 divided doses a day or as a sustained form. Administration may be effected by injection, etc.

For administration, the compound used in the invention can be given in the form of a conventional pharmaceutical preparation which contains said compound, as an active ingredient, in admixture with a pharmaceutically acceptable carrier , e.g. organic or inorganic, solid or liquid excipients suitable for the desired mode of administration. Such a preparation may be in a solid form, e.g. a solid from which a solution can be prepared before use, etc. or in a liquid form, e.g. solution, emulsion, suspension, etc. Suitable carriers include starch, lactose, glucose, sucrose, dextrin cellulose, paraffin, aliphatic glyceride, water, alcohol, acacia etc. The above preparation may also contain an auxiliary substance, stabilizer, emulsifier, lubricant, binder, pH-adjuster, isotonic agent and other conventional additives, as necessary.

The present invention is illustrated in more detail by way of the following Examples and Test Examples.

Example 1

Dimethylcyclodextrin		100 mg
Physiological saline	q.s. to	10 ml

The above ingredients are brought into solution in a conventional manner to form an injectable solution.

Test Example 1

Beagle dogs (weight: 7-8 kg) were divided into groups. The animals were kept away from food and water for 17 hours before the administration of the test compositions. A Ringer solution (25 mg/kg) was intravenously administered over one hour (for water-loading) and, after 30 minutes, a solution of dimethyl-α-cyclodextrin [a mixture mainly comprising hexakis(2,6-di-O-methyl)-α-cyclodextrin and pentakis(2,6-di-O-methyl)-mono(2,3,6-tri-O-methyl)-α-cyclodextrin; hereinafter referred to as DMCD] (5 mg/kg) in the Ringer solution was intravenously administered. The control group received the same amount of Ringer solution.

Urine samples were collected using a catheter at 30 minute intervals and assayed for the amount of electrolytes (sodium, potassium and chloride). Also, the total amount of excretion of each item, respectively, from the time of administration and up to 120 minutes thereafter were measured. The results are shown in Table 1. In addition, urine and serum creatinine concentrations were measured at an appropriate time from which values of creatinine clearance

(glomerular filtration) were calculated. The results are shown in Table 2.

Table 1

	Urine(ml)	Na(mEq)	K(mEq)	Cl(mEq)
Control (n=6)	26.9±19.3 (S.D.)	4.4±2.2	1.3±0.5	4.9±1.7
	**	*	*	*
DMCD (n=3)	61.3±3.6	12.7±3.0	3.8±1.1	13.6±3.1

Dannet Method: * P<0.01, ** P<0.05

Table 2

	Creatinine Clearance (ml/kg/min)	
After:	60 min	120 min
Control (n=6)	2.47±0.76 (S.D.)	2.67±0.74
	**	
DMCD (n=3)	3.83±0.63	3.50±0.29

Test Example 2

Male rats (Crj; weight 100-150 g) were divided into groups. After receiving the test compositions, they were left in cages. Cumulative amount of urine was weighed after 3 hours without food and water (3 hr Urine) and after an additional 21 hours with food and water (21 hr Urine), giving 24 hr urine as the total amount. Further, 21 hr urine was

assayed for osmotic pressure using an osmometer (OM-801*, Asahi Lifescience). DMCD, hexakis(2,6-di-O-methyl-α-cyclodextrin [purified from DMCD as a mixture; hereinafter referred to as Compound I] and pentakis(2,6-di-O-methyl)-mono(2,3,6-tri-O-methyl)-α-cyclodextrin [purified from DMCD as a mixture; hereinafter referred to as Compound II], dissolved in the physiological saline were used as the test compounds and administered at a rate of 5 mg/kg via a caudal vein. The control group received the physiological saline. The results are shown in Table 3.

Table 3

	Urine(ml)	Osmotic Pressure(osm/kg)
Control (n=6)	10.5±1.3 (S.D.)	2.23±0.55
DMCD 1 mg/kg (n=3)	16.0±2.2	1.40±0.17
Compound I 1 mg/kg (n=3)	14.0±4.0	1.65±0.41
Compound I 5 mg/kg (n=3)	15.4±1.4	1.41±0.23
Compound II 2 mg/kg (n=3)	14.0±5.2	1.68±0.65
Compound II 5 mg/kg (n=3)	16.4±0.8	1.31±0.39

*Trade mark

The above results indicate that the compounds used in the invention have excellent diuretic action.

Claims:

1. A pharmaceutical composition for diuresis improvement comprising a cyclodextrin or a derivative thereof in association with a pharmaceutically acceptable carrier, diluent or excipient.

2. A pharmaceutical composition according to claim 1, in which the derivative is selected from the group consisting of etherified cyclodextrins, branched cyclodextrins, acylated cyclodextrins and sulfur-containing cyclodextrins.

3. A pharmaceutical composition according to claim 1, in which the derivative is selected from the group consisting of dimethylcyclodextrin.

4. A pharmaceutical composition according to claim 1, for glomerular filtration enhancement.

5. The use of a pharmaceutical composition comprising a cyclodextrin or a derivative thereof in association with a pharmaceutically acceptable carrier, diluent or excipient for diuresis improvement.