Title: USE OF ADENOSINE A1 ANTAGONIST IN RADIOCONTRAST MEDIA INDUCED NEPHROPATHY

Abstract: The present invention relates to pharmaceutical combinations comprising a therapeutically effective amount of at least one selective adenosine A1 antagonist and at least one radiocontrast media. In particular, the present invention relates to pharmaceutical combinations comprising 4-[(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)aminol]-trans-cyclohexanol methanesulfonate and/or (4S)-4-hydroxy-1-(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-L-prolinamide methanesulfonate as selective adenosine A1 antagonists and at least one radiocontrast media. The invention also relates to the use of said combinations in the manufacture of a medicament for the treatment of radiocontrast media induced nephropathy. Furthermore, the invention is relating to a kit comprising a therapeutically effective amount of said combination of at least one selective adenosine A1 antagonist and at least one radiocontrast media.
USE OF ADENOSINE A1 ANTAGONISTS IN RADIOCONTRAST MEDIA INDUCED NEPHROPATHY

FIELD OF INVENTION

The present invention relates to pharmaceutical combinations comprising a therapeutically effective amount of at least one selective adenosine A1 receptor antagonist and at least one radiocontrast media (RM). The invention also relates to the use of said combinations in the manufacture of a medicament for the treatment of radiocontrast media induced nephropathy. Furthermore, the invention relates to a kit comprising said combinations.

BACKGROUND OF THE INVENTION

Interventional techniques, fast multislice computer tomographies and new 3D reconstruction techniques have increased the use of iodinated intravascular radiocontrast media (RM) over the last decades. The majority of examinations require iodinated RM for accurate and safe diagnosis and interventional procedures. Today approximately 60 million dosages are applied every year worldwide (Andrew, 2004). Radiocontrast media can lead to a decline of excretory renal function that starts soon after administration. The renal dysfunction can be transient, persistent or even irreversible. Hence, the use of radiocontrast media has been associated with increased in-hospital morbidity, mortality, and cost of medical care and long admissions, especially in patients requiring dialysis. Radiocontrast media induced nephropathy (CIN) is therefore a clinically important problem. CIN is a structural damage of the kidney. The definition of CIN varies. It can be defined as acute aggravation of renal functionality after application of RM, induced as proximate cause to the exclusion of alternative etiologies. The most common definition of a minor effect is an increase in serum creatinine greater than 25% or 44 mol/l (0.5 mg/dl) after the intravascular administration of a RM. A major effect is defined as increase in serum creatinine greater than 50% or 88 mmol/l (1 mg/dl). The pathogenesis of CIN is not fully understood. It is believed, that two main factors, hemodynamic as well as tubular effects, are involved. Application of RM leads to a change in renal hemodynamics, above all to a decrease in the glomerular filtration rate (GFR). GFR is the rate of ultra filtration of plasma across the walls of the glomerular capillaries and measurement of total GFR of both kidneys provides a sensitive
index of overall renal excretory function. The glomerular filtration rate is calculated by comparing urine creatinine levels with the blood test results. A GFR value (see http://www.fpnotebook.com²) in a range of 97-137 ml/min/1.73 m² is adequate for a male human and of 88-128 ml/min/1.73 m is adequate for a female human, whereas a GFR lower than 15 ml/min/1.73 m² leads to kidney failure. A decrease in GFR induced by application of RM is considered to be the main cause for the development of CIN. Along the renal tubular system, substances like RM that are not reabsorbed become increasingly concentrated. Up to 99% of renal fluids are usually taken up by the action of manifold cellular and paracellular mechanisms. This means that the urine concentration of RM can increase by a factor of 100. Along with the continuous concentration process, tubular fluid containing RM will become increasingly viscous and can lead to tubular obstruction (Ueda, 1993³). Inevitably, intrarenal pressure increases as well, since the kidney cannot expand due to the surrounding capsule. As a consequence, renal perfusion pressure for the renal medulla may no longer be sufficient to warrant sufficient perfusion. In the kidney, activation of A1AR in afferent glomerular arterioles has been suggested to contribute to tubuloglomerular feedback (TGF), which is a strategic feedback mechanism, designed to control tubular flow and regional perfusion. The vasoconstriction elicited by elevations in [NaCl] in the macula densa region of the nephron. A role of adenosine in TGF response mediation is consistent with its effect to cause vasoconstriction. In addition to its vasoconstrictor effect, A1 receptor stimulation contracts mesangial cells in the glomerulus (Olivera, 1989¹). Acute renal failure caused by the injection of RM has been recognized for many years as a complication in diagnostic and interventional procedures. The incidence of acute renal failure directly induced by RM lies at approximately 10-15%, while the incidence of CIN defined by clinically significant increases in serum creatinine is as high as 22% (Porter, 1989⁵). The peak creatinine concentration occurs within 3-5 days of exposure to the contrast media and usually resolves satisfactorily, but in up to 10% of at risk patients, dialysis is required. Preexisting renal insufficiency reduced intravascular volume and additional underlying diseases (e.g. hypertension, diabetes mellitus) are said to be some of the leading risk factors for radiocontrast media induced nephropathy. The osmolality, the measurement of the number of molecules and particles in a solution per kilogram of water, of the RM is regarded to be of great importance in radiocontrast induced nephropathy. The incidence of nephropathy induced by low-osmolar RM is low in the general population and has been calculated to be less than 2 % (Nikolsky, 2003⁶).
The adenosine production is one of the discussed mechanisms behind CIN. Adenosine is an endogenous neuromodulator with predominantly inhibitory effects on the CNS, heart, kidneys and other organs. It is a naturally occurring nucleoside, which exerts its biological effects by interacting with a family of adenosine receptors known as A1, A2a, A2b, and A3, all of which modulate important physiological processes. Selective A1 adenosine receptor antagonists (A1AR) have pronounced effects on the kidney, and have shown to be potent diuretics and natriuretics with little effect on potassium excretion. Thus, they are renal protective, useful for the treatment of renal failure, renal dysfunction, nephritis, hypertension, and edema. The kidney produces adenosine constitutively to regulate glomerular filtration and electrolyte reabsorption mediated by the adenosine A1 receptor system. The A1 adenosine receptor has been found to govern the vasoconstriction response of the afferent glomerular arteriole. Adenosine causes a reduction in the blood flow to the kidney, and thus a reduction in the glomerular filtration rate and the renal blood flow. Inhibition of the A1 receptor will heighten the glomerular filtration rate, and correspondingly increase the rate of urine formation. The application of adenosine receptor antagonists has been implicated in protection from acute renal failure. The adenosine receptor antagonists aminophylline (combination of theophylline and ethylenediamine 2:1) and theophylline (which has been found to non-selectively antagonize adenosine receptors in the brain) were evaluated as potential agents to protect against radiocontrast media induced nephropathy (Shammas, 2001; Welch, 2002; Huber, 2002°). Aminophylline does not appear to add a protective role in preventing radiocontrast media induced nephropathy while theophylline was effective in preventing radiocontrast media induced nephropathy impaired renal excretory, endocrine and tubular function. These results suggest that adenosine may play a role in the pathogenesis of CIN and that application of non-selective adenosine receptor antagonists has been implicated in protection from acute renal failure associated with RM treatment. Erley (1994④) investigated the influence of the non-selective adenosine antagonist theophylline on the glomerular filtration rate after the application of RM and allocates adenosine a major role in CIN. Furthermore, Arakawa (1996⑤) describe the role of adenosine in the renal responses to the contrast medium iohexol in dogs with and without pre-existing renal insufficiency. Arakawa indicates that in normal renal function, iohexol elicits renal vasodilation by activating mainly the adenosine A2 receptors. Whereas in impaired renal function, iohexol induces both A2 and A1 activation. Arakawa proposes the adenosine A2 receptors to be associated with the initial renal vasodilation, and the adenosine A1 receptors to be responsible for the sustained aggravation of renal hemodynamics. Yao (2000⑥) investigated the influence of the selective adenosine A1 antagonist KW-3902 on radiocontrast media induced nephropathy in rats with chronic nitric
oxide deficiency. Yao suggested adenosine influencing the pathogenesis of CIN via the activation of the A1 receptors. Greiner (2005\textsuperscript{11}) studied the influence on theophylline and acetylcystein separately and in combination on radiocontrast media induced nephropathy in intensive care patients and corroborates the prophylactic properties of theophylline in CIN. Lee (2006\textsuperscript{12}) concludes that renal A1 adenosine receptors being only partially responsible in the pathogenesis of radiocontrast nephropathy. In experiments with renal A1 adenosine receptors knockout mice was found, that these mice are protected from acute renal failure induced by RM injection. Direct tubular toxicity seemed, however, not to be modulated by renal A1 adenosine receptors. Patent application EP 1 386 609 (CV Therapeutics\textsuperscript{13}) describes methods for restoring diuretic and renal function comprising adenosine A1 antagonist in combination with a diuretic. Patent application WO 99/31101 (Univ. South Florida \textsuperscript{14}) discloses xanthine derivatives as adenosine A1 receptor antagonists. Further on, radiolabelled derivatives and a method of imaging the adenosine A1 receptor antagonists for medical diagnostic purposes are mentioned.

SUMMARY OF THE INVENTION

A\textsubscript{1}AR have been previously shown to possess protective effects in several nephrotoxic models of acute renal failure. Increased release of renal adenosine and stimulation of renal adenosine receptors have been proposed to be among the major reasons in development of radiocontrast media induced acute renal failure. We now surprisingly found that administration of selective A1 receptor antagonists of formula I especially, is beneficial in preventing the risk of CIN development and/or need of dialysis in patients who receive radiocontrast media. We now surprisingly found that administration of selective A1 receptor antagonists of formula I especially, is beneficial in preventing the risk of side effects and end-organ damage like CIN development and/or need of dialysis in patients who receive radiocontrast media.

The treatment of a specific group of seriously ill patients suffering from certain long term renal disorders with selective adenosine A1 antagonists in order to cure or improve these renal disorders is proposed by the state of the art (see e.g. WO 2004/094428\textsuperscript{15}). We now surprisingly found that the administration of selective A1 receptor antagonists of formula I especially, is beneficial in preventing the risk of CIN development and/or need of dialysis in all groups of patients who receive radiocontrast media, including healthy patients as well as patients already suffering from renal disorders, e.g. renal failure and other renal disorders.
It is therefore an object of the present invention to use a therapeutically effective amount of at least one selective adenosine A1 receptor antagonist for the manufacture of a medicament for the treatment of nephropathy induced by at least one radiocontrast media, for the increase in serum creatinine levels, for the decrease in renal blood flow, as well as for the prevention of dialysis requirement caused by radiocontrast media induced nephropathy, in mammals and humans.

A further object of the invention is pertaining to pharmaceutical combination comprising a therapeutically effective amount of at least one selective adenosine A1 receptor antagonist and a radiocontrast media.

A further object of the invention is pertaining to a kit comprising a therapeutically effective amount of at least one selective adenosine A1 receptor antagonist and a radiocontrast media.

The at least one A1AR antagonist which can be used according to the present invention may be selected from the group consisting of a compound of formula I

![Chemical Structure](image)

wherein

R1 and R2 are each independently selected from a hydrogen atom, an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety or together form an optionally substituted heterocyclic ring;

R3 is selected from a hydrogen atom or an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety;

R4 and R5 are each independently selected from a halogen atom, a hydrogen atom or an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety, or R4 and R5 together form an optionally substituted heterocyclic or optionally substituted carbocyclic ring;
and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof,
for the manufacture of a medicament for the prevention of nephropathy induced by at least one
RM in mammals or humans.
and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof.

In particular, the present invention relates to a pharmaceutical combination consisting of a fixed
combination of 4-[(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-trans-cyclohexanol
methanesulfonate or (4S)-4-hydroxy-1-(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-L-prolinamide
methanesulfonate with at least one RM.

The at least one RM which can be used according to the present invention may be an iodinated
or gadolinium-based radiocontrast media selected from the group consisting of bunaiod, 
obilgram, bilimiro, bilopaque, cholimil, ethiodol, diatrace, dionosil, fatignost, gadobutrol,
gadodiamide, gadopentetate dimeglumine, gastrografin, hexabrix, hippodin, mangafodipir,
amidotrizoate, ethiodized oil, imagopaque, iodamide, iodipamide, iodixanol, iodophene, 
iophendylate, iomerin, iomeprol, iopamidol, iopanoic acid, iopiperidol, iophendylate, iopromide,
iopydol, iosimel, iothalamic acid, iotrolan, ioversol, ixilan, ioxaglic acid, isopaque, ipodate, 
meglumine iothalamate, meglumine acetrizoate, meglumine diatrizoate, metrizamide, myelotrace, 
onnipaque, osbil, optiray, optojod, opacoron, perflutren, phenobutidil, phentetiothalein sodium, 
pridax, propyliodone, skiodan, sodium iodomethamate, sodium diatrizoate, telepaque, teridax, 
tetabrom, thorotrace, triognost, 1,3,5-Tri-n-hexyl-2,4,6-triiodobenzene, tyropanoate, visipaque or 
exetix, and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention pertains to the use of a therapeutically effective amount of at least one
selective adenosine A1 antagonist for the manufacture of a medicament for the prevention of
nephropathy induced by at least one radiocontrast media in mammals or humans. The invention
pertains thus to the use of a therapeutically effective amount of at least one selective adenosine
A1 antagonist of formula I
wherein
R1 and R2 are each independently selected from a hydrogen atom, an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety or together form an optionally substituted heterocyclic ring;
R3 is selected from a hydrogen atom or an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety;
R4 and R5 are each independently selected from a halogen atom, a hydrogen atom or an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety, or R4 and R5 together form an optionally substituted heterocyclic or optionally substituted carbocyclic ring;
and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof,
for the manufacture of a medicament for the prevention of nephropathy induced by at least one radiocontrast media in mammals or humans.

Furthermore, the invention relates to the use of a therapeutically effective amount of at least one selective adenosine A1 antagonist for the manufacture of a medicament for the prevention of increase in serum creatinine levels induced by at least one radiocontrast media in mammals or humans. The invention pertains thus to the use of a therapeutically effective amount of at least one selective adenosine A1 antagonist of formula I, as defined above, for the manufacture of a medicament for the prevention of increase in serum creatinine levels induced by at least one radiocontrast media, preferably of a transient, persistent or irreversible increase in serum creatinine levels induced by radiocontrast media in mammals or humans.

Furthermore, the invention relates to the use of a therapeutically effective amount of at least one selective adenosine A1 antagonist for the manufacture of a medicament for the prevention of decrease in renal blood flow induced by at least one radiocontrast media. The invention pertains thus to the use of a therapeutically effective amount of at least one selective adenosine A1
antagonist of formula I, as defined above, for the manufacture of a medicament for the prevention of decrease in renal blood flow induced by at least one radiocontrast media, preferably of a transient, persistent or irreversible decrease in renal blood flow induced by radiocontrast media in mammals or humans.

Furthermore, the invention relates to the use of a therapeutically effective amount of at least one selective adenosine A1 antagonist for the manufacture of a medicament for the prevention of dialysis requirement caused by radiocontrast media induced nephropathy, said CIN may be transient, persistent or irreversible, in mammals or humans. The invention pertains thus to the use of a therapeutically effective amount of at least one selective adenosine A1 antagonist of formula I, as defined above, for the manufacture of a medicament for the prevention of a risk or need of dialysis in a human or mammalian patient, preferably of transient, persistent or irreversible dialysis, said patient being subject to receive radiocontrast media.

The present invention further relates to a pharmaceutical combination of a therapeutically effective amount of at least one selective adenosine A1 antagonist, and at least one radiocontrast media, wherein the pharmaceutical combination being suitable for simultaneous, separate or step-wise administration to humans or mammals.

Furthermore, the present invention relates to a kit comprising a therapeutically effective amount of at least one selective adenosine A1 antagonist, and at least one radiocontrast media, wherein the pharmaceutical combination being suitable for simultaneous, separate or step-wise administration to humans or mammals.

The A1AR which can be used according to the present invention may be selected from formula I

![Chemical Structure](image)

wherein
R1 and R2 are each independently selected from a hydrogen atom, an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylarylo moiety or together form an optionally substituted heterocyclic ring; R3 is selected from a hydrogen atom or an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylarylo moiety; R4 and R5 are each independently selected from a halogen atom, a hydrogen atom or an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylarylo moiety, or R4 and R5 together form an optionally substituted heterocyclic or optionally substituted carbocyclic ring; preferably wherein
R1 and R2 are each independently selected from a hydrogen atom, an optionally substituted alkyl or together form an optionally substituted heterocyclic ring; R3 is a hydrogen atom or an optionally substituted aryl; R4 and R5 are each independently selected from a halogen atom or a hydrogen atom;
more preferably wherein
R1 is a hydrogen and R2 is an optionally substituted cyclohexyl ring, or R1 and R2 together form an optionally substituted pyrrolidine ring; R3 is a phenyl ring; R4 and R5 are each a hydrogen atom;
and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof.

In a preferred embodiment, A1ARs according to the present invention may be selected from 4-[(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-trans-cyclohexanol methanesulfonate or (4S)-4-hydroxy-1-(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-L-prolinamide methanesulfonate and/or a prodrug, and/or a solvate thereof.

The A1ARs suitable for use herein are described within the international patent applications WO 99/62518, WO 01/39777, WO 02/057267 and WO 2004/094428 (Osi Pharmaceuticals and Solvay Pharmaceuticals®).

The RM which can be used according to the present invention may be an iodinated or gadolinium-based radiocontrast media selected from the group consisting of bunaid, biligram, bilimiro, bilopaque, cholimil, ethiodol, diatrat, dionosil, falignost, gadobutrol, gadodiamide, gadopentetate dimeglumine, gastrografin, hexabrix, hippodin, mangafodipir, amidotrizoate, ethiodized oil, imagopaque, iodamide, iodipamide, iodixanol, iodophene, iophendylate, iomeron, iomeprol, iopamidol, iopanoic acid, iopiperidol, iophendylate, iopromide, iopydol, iosimenol, iothalamic acid, iotrolan, ioversol,ioxilan, ioxaglic acid, isopaque, ipodate, meglumine
iothalamate, meglumine acetrizoate, meglumine diatrizoate, metrizamide, myelotраст, omnipaque, osbil, optiray, optojod, opacoron, perflu tren, phenobutiodil, phentetiothalein sodium, priodax, propylidone, skiodan, sodium iodomethamate, sodium diatrizoate, telepaque, teridax, tetrabrom, thorotrast, triognost, 1,3,5-Tri-n-hexyl-2,4,6-triiodobenzene, tyropanoate, visipaque or xenetix, and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof.

Preferred RM include xenetix, omnipaque or visipaque.

Some examples (Schering, Bracco Industria Chimica, Univ. California, Nyegaard, Cook Imaging Corporation, Mallinckrodt, Eprova, Nycomed and Savag¹⁶) of RM suitable for use herein are described within European patent applications EP 0 022 744, EP 0 023 992, EP 0 026 281, EP 0 033 426, EP 0 108 638 and EP 0 317 492, the international applications WO 87/00757 and WO 89/08101, the US patents US 2,776,241, US 3,290,366, US 3,360,436, and US 5,349,085, the British application GB 1 321 591 as well as within the German patents DE 2 547 789, DE 2 726 196 and DE 2 909 439, without limiting the group of RM.

4-[(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-trans-cyclohexanol methanesulfonate will hereafter also be abbreviated as substance 1 and (4S)-4-hydroxy-1-(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-L-prolinamide methanesulfonate will hereafter also be abbreviated as substance 2.

In a preferred embodiment, the invention pertains to a use of substance 1 and bunaiod, or substance 1 and biligram, or substance 1 and bilimiro, or substance 1 and bilopaque, or substance 1 and cholimil, or substance 1 and ethiodol, or substance 1 and diatras, or substance 1 and dionosil, or substance 1 and falignost, or substance 1 and gadobutrol, or substance 1 and gadodiamide, or substance 1 and gadopentetate dimeglumine, or substance 1 and gastrografin, or substance 1 and hexabrix, or substance 1 and hippodin, or substance 1 and mangafodipir, or substance 1 and amidotrizoate, or substance 1 and ethiodized oil, or substance 1 and imagopaque, or substance 1 and iodamide, or substance 1 and iodipamide, or substance 1 and iodixanol, or substance 1 and iodophene, or substance 1 and iophendylate, or substance 1 and imeron, or substance 1 and iomeprol, or substance 1 and iopamidol, or substance 1 and iopanoic acid, or substance 1 and iopiperidol, or substance 1 and iophendylate, or substance 1 and iopromide, or substance 1 and iopydol, or substance 1 and iosimenol, or substance 1 and iothalamic acid, or substance 1 and iotrolan, or substance 1 and ioversol, or substance 1 and
ioxilan, or substance 1 and ioxaglic acid, or substance 1 and isopaque, or substance 1 and ipodate, or substance 1 and meglumine iothalamate, or substance 1 and meglumine acetrizoate, or substance 1 and meglumine diatrizoate, or substance 1 and metrizamide, or substance 1 and myelotrat, or substance 1 and omnipaque, or substance 1 and osbil, or substance 1 and optiray, or substance 1 and optojod, or substance 1 and opacoron, or substance 1 and perflutren, or substance 1 and phenobutiodil, or substance 1 and phentetiothalein sodium, or substance 1 and priodax, or substance 1 and propylidone, or substance 1 and skiodan, or substance 1 and sodium iodomethamate, or substance 1 and sodium diatrizoate, or substance 1 and telepaque, or substance 1 and teridax, or substance 1 and tetrabrom, or substance 1 and thorotrat, or substance 1 and triognost, or substance 1 and 1,3,5-Tri-n-hexyl-2,4,6-triiodobenzene, or substance 1 and tyropanoate, or substance 1 and visipaque, or substance 1 and xenetix. In a preferred embodiment, the invention pertains to a pharmaceutical combination of substance 1 and bunaiod, or substance 1 and biligram, or substance 1 and bilimiro, or substance 1 and bilopaque, or substance 1 and cholimil, or substance 1 and ethiodol, or substance 1 and diatrat, or substance 1 and dionosil, or substance 1 and falgnost, or substance 1 and gadobutrol, or substance 1 and gadodiamide, or substance 1 and gadopentetate dimeglumine, or substance 1 and gastrografen, or substance 1 and hexabrix, or substance 1 and hippodin, or substance 1 and mangafodipir, or substance 1 and amidotrizoate, or substance 1 and ethiodized oil, or substance 1 and imagopaque, or substance 1 and iodamide, or substance 1 and iodipamide, or substance 1 and iodixanol, or substance 1 and iodophene, or substance 1 and iophendylate, or substance 1 and isomeron, or substance 1 and iodemprol, or substance 1 and iopamidol, or substance 1 and iopanoic acid, or substance 1 and iopiperidol, or substance 1 and iophendylate, or substance 1 and iopromide, or substance 1 and iopydol, or substance 1 and iosimenol, or substance 1 and iothalamic acid, or substance 1 and iotrolan, or substance 1 and ioversol, or substance 1 and ioxilan, or substance 1 and ioxaglic acid, or substance 1 and isopaque, or substance 1 and ipodate, or substance 1 and meglumine iothalamate, or substance 1 and meglumine acetrizoate, or substance 1 and meglumine diatrizoate, or substance 1 and metrizamide, or substance 1 and myelotrat, or substance 1 and omnipaque, or substance 1 and osbil, or substance 1 and optiray, or substance 1 and optojod, or substance 1 and opacoron, or substance 1 and perflutren, or substance 1 and phenobutiodil, or substance 1 and phentetiothalein sodium, or substance 1 and priodax, or substance 1 and propylidone, or substance 1 and skiodan, or substance 1 and sodium iodomethamate, or substance 1 and sodium diatrizoate, or substance 1 and telepaque, or substance 1 and teridax, or substance 1 and tetrabrom, or substance 1 and thorotrat, or substance 1 and triognost, or
substance 1 and 1,3,5-Tri-n-hexyl-2,4,6-triiodobenzene, or substance 1 and tyropanoate, or substance 1 and visipaque, or substance 1 and xenetix. In a preferred embodiment, the invention pertains to a kit comprising substance 1 and bunaiod, or substance 1 and biligram, or substance 1 and bilimiro, or substance 1 and bilopaque, or substance 1 and cholimil, or substance 1 and ethiodol, or substance 1 and diatras, or substance 1 and dionosil, or substance 1 and falignost, or substance 1 and gadobutrol, or substance 1 and gadodiamide, or substance 1 and gadopentetate dimeglumine, or substance 1 and gastrografin, or substance 1 and hexabrix, or substance 1 and hippocin, or substance 1 and mangafodipir, or substance 1 and amidotrizoate, or substance 1 and ethiodized oil, or substance 1 and imagopaque, or substance 1 and iodamide, or substance 1 and iodipamide, or substance 1 and iodixanol, or substance 1 and iodophene, or substance 1 and iopendylate, or substance 1 and iomeron, or substance 1 and iomeprol, or substance 1 and iopamidol, or substance 1 and iopanoic acid, or substance 1 and iopiperidol, or substance 1 and ioprendylate, or substance 1 and iopromide, or substance 1 and iopydol, or substance 1 and iosimenol, or substance 1 and iothalamic acid, or substance 1 and iotrolan, or substance 1 and ioversol, or substance 1 and ioxilan, or substance 1 and ioxaglic acid, or substance 1 and isopaque, or substance 1 and ipodate, or substance 1 and meglumine iothalamate, or substance 1 and meglumine acetrizoate, or substance 1 and meglumine diatrizoate, or substance 1 and metrizamide, or substance 1 and myelotrat, or substance 1 and omnipaque, or substance 1 and osbil, or substance 1 and optiray, or substance 1 and optojod, or substance 1 and opacoron, or substance 1 and perflutren, or substance 1 and phenobutiodil, or substance 1 and phentetiothalein sodium, or substance 1 and priodax, or substance 1 and propylidione, or substance 1 and skiodan, or substance 1 and sodium iodomethamate, or substance 1 and sodium diatrizoate, or substance 1 and telepaque, or substance 1 and teridax, or substance 1 and tetrabrom, or substance 1 and thorotrat, or substance 1 and triognost, or substance 1 and 1,3,5-Tri-n-hexyl-2,4,6-triiodobenzene, or substance 1 and tyropanoate, or substance 1 and visipaque, or substance 1 and xenetix.

In a preferred embodiment, the invention pertains to a use of substance 2 and bunaiod, or substance 2 and biligram, or substance 2 and bilimiro, or substance 2 and bilopaque, or substance 2 and cholimil, or substance 2 and ethiodol, or substance 2 and diatras, or substance 2 and dionosil, or substance 2 and falignost, or substance 2 and gadobutrol, or substance 2 and gadodiamide, or substance 2 and gadopentetate dimeglumine, or substance 2 and gastrografin, or substance 2 and hexabrix, or substance 2 and hippocin, or substance 2 and mangafodipir, or substance 2 and amidotrizoate, or substance 2 and ethiodized oil, or substance 2 and
imagopaque, or substance 2 and iodamide, or substance 2 and iodipamide, or substance 2 and iodixanol, or substance 2 and iodophene, or substance 2 and iopamidol, or substance 2 and iomeron, or substance 2 and iomeprol, or substance 2 and iopamide, or substance 2 and iopiperidol, or substance 2 and iop香港, or substance 2 and ipodate, or substance 2 and meglumine iothalamate, or substance 2 and meglumine acetrizoate, or substance 2 and meglumine diatrizoate, or substance 2 and metrizamide, or substance 2 and myelotrat, or substance 2 and omnipaque, or substance 2 and osbil, or substance 2 and optiray, or substance 2 and optojod, or substance 2 and opacoron, or substance 2 and perfluiren, or substance 2 and phenobutrol, or substance 2 and phenetiothalein sodium, or substance 2 and priodax, or substance 2 and propyliodone, or substance 2 and skiodan, or substance 2 and sodium iodomethamate, or substance 2 and sodium diatrizoate, or substance 2 and telepaque, or substance 2 and teridax, or substance 2 and tetrabrom, or substance 2 and thorotrast, or substance 2 and triognost, or substance 2 and 1,3,5-Tri-n-hexyl-2,4,6-triiodobenzene, or substance 2 and tyropanoate, or substance 2 and visipaque, or substance 2 and xenetix. In a preferred embodiment, the invention pertains to a pharmaceutical combination of substance 2 and bunaiod, or substance 2 and biligram, or substance 2 and bilimiro, or substance 2 and bilopaque, or substance 2 and cholimil, or substance 2 and ethiodol, or substance 2 and diatrac, or substance 2 and doinosil, or substance 2 and failignost, or substance 2 and gadobutrol, or substance 2 and gadodiamide, or substance 2 and gadopentetate dimeglumine, or substance 2 and gastrografin, or substance 2 and hexabrix, or substance 2 and hippodin, or substance 2 and mangafodipir, or substance 2 and amidotrizoate, or substance 2 and ethiodized oil, or substance 2 and imagopaque, or substance 2 and iodamide, or substance 2 and iodipamide, or substance 2 and iodixanol, or substance 2 and iodophene, or substance 2 and iopamidol, or substance 2 and iomeprol, or substance 2 and iopiperidol, or substance 2 and iop香港, or substance 2 and ipodate, or substance 2 and meglumine iothalamate, or substance 2 and meglumine acetrizoate, or substance 2 and meglumine diatrizoate, or substance 2 and metrizamide, or substance 2 and myelotrat, or substance 2 and
omnipaque, or substance 2 and osbil, or substance 2 and optiray, or substance 2 and optojod, or substance 2 and opacoron, or substance 2 and perflu tren, or substance 2 and phenobutidil, or substance 2 and phentetiothalein sodium, or substance 2 and priodax, or substance 2 and propyliodone, or substance 2 and skiodan, or substance 2 and sodium iodomethamate, or substance 2 and sodium diatrizoate, or substance 2 and telepaque, or substance 2 and teridax, or substance 2 and tetrabrom, or substance 2 and thorotrast, or substance 2 and triognost, or substance 2 and 1,3,5-Tri-n-hexyl-2,4,6-triodobenzene, or substance 2 and tyropanoate, or substance 2 and visipaque, or substance 2 and xenetix. In a preferred embodiment, the invention pertains to a kit comprising substance 2 and bunaiod, or substance 2 and biligram, or substance 2 and bilimiro, or substance 2 and bilopaque, or substance 2 and cholimil, or substance 2 and ethiodol, or substance 2 and diatrazt, or substance 2 and dionosil, or substance 2 and falignost, or substance 2 and gadobutrol, or substance 2 and gadodiamide, or substance 2 and gadopentetate dimeglumine, or substance 2 and gastrografin, or substance 2 and hexabrix, or substance 2 and hippodin, or substance 2 and mangafodipir, or substance 2 and amidotrizoate, or substance 2 and ethiodized oil, or substance 2 and imagopaque, or substance 2 and iodamide, or substance 2 and iodipamide, or substance 2 and iodixanol, or substance 2 and iodophene, or substance 2 and iophendylate, or substance 2 and iomeron, or substance 2 and iomeprol, or substance 2 and iopamidol, or substance 2 and iopanoic acid, or substance 2 and iopiperidol, or substance 2 and iophendylate, or substance 2 and iopromide, or substance 2 and iopydol, or substance 2 and iosimenol, or substance 2 and iothalamic acid, or substance 2 and iotrolan, or substance 2 and ioversol, or substance 2 and ioxilan, or substance 2 and ioxaglic acid, or substance 2 and isopaque, or substance 2 and ipodate, or substance 2 and meglumine iothalamate, or substance 2 and meglumine acetrizoate, or substance 2 and meglumine diatrizoate, or substance 2 and metrizamide, or substance 2 and myelotраст, or substance 2 and omnipaque, or substance 2 and osbil, or substance 2 and optiray, or substance 2 and optojod, or substance 2 and opacoron, or substance 2 and perflu tren, or substance 2 and phenobutidil, or substance 2 and phentetiothalein sodium, or substance 2 and priodax, or substance 2 and propyliodone, or substance 2 and skiodan, or substance 2 and sodium iodomethamate, or substance 2 and sodium diatrizoate, or substance 2 and telepaque, or substance 2 and teridax, or substance 2 and tetrabrom, or substance 2 and thorotrast, or substance 2 and triognost, or substance 2 and 1,3,5-Tri-n-hexyl-2,4,6-triodobenzene, or substance 2 and tyropanoate, or substance 2 and visipaque, or substance 2 and xenetix.
By a "therapeutically effective amount" of a drug or pharmacologically active agent is meant a nontoxic but sufficient amount of the drug or agent to provide the desired effect. In the combination therapy of the present invention, a "therapeutically effective amount" of one component of the combination is the amount of that compound that is effective to provide the desired effect when used in combination with the other components of the combination. The amount that is "effective" will vary from subject to subject, depending on the age and general condition of the individual, the particular active agent or agents, and the like. It thus is not always possible to specify an exact "therapeutically effective amount". However, an appropriate "therapeutically effective amount" in any individual case may be determined by an ordinary skill artisan using routine experimentation.

The at least one RM is not earlier administered until the plasma level of the at least one selective adenosine A1 receptor antagonist has reached a concentration of 10-500 ng/ml. The invention also pertains to any arbitrary concentration or concentration ranges, which lie within the range of 10-500 ng/ml. In a preferred embodiment, the at least one selective adenosine A1 antagonist has a concentration of 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, and 500 ng/ml, and any arbitrary concentration or concentration ranges, which lie in any ranges defined by two of the before mentioned concentration values, where the lower limit of said range is defined by the minor value and the upper limit of said range by the upper value, e.g. a range of 110-180 ng/ml, 370-390 ng/ml, 10-150 ng/ml, etc. The invention thus pertains to the use comprising the at least one radiocontrast media to be not earlier administered until the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist is sufficient to provide a plasma level concentration of 10-500 ng/ml, preferably 20-400 ng/ml, more preferably 30-300 ng/ml. The invention thus further pertains to a pharmaceutical combination comprising the at least one radiocontrast media to be not earlier administered until the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist is sufficient to provide a plasma level concentration of 10-500 ng/ml, preferably 20-400 ng/ml, more preferably 30-300 ng/ml. The invention further pertains to a use comprising the at least one radiocontrast media to be not earlier administered until the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist is sufficient to provide a plasma level concentration of 10-500 ng/ml, preferably 20-400 ng/ml, more preferably 30-300 ng/ml. The invention further pertains to a pharmaceutical combination comprising the at least one radiocontrast media to be not earlier administered until the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist is sufficient to provide a plasma level concentration of 10-500 ng/ml, preferably 20-400 ng/ml, more preferably 30-300 ng/ml.
administered until the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist is sufficient to provide a plasma level concentration of 10-500 ng/ml, preferably 20-400 ng/ml, more preferably 30-300 ng/ml.

The time period of application of the maintenance dosage of the at least one selective A1 adenosine antagonist is sufficient to maintain the plasma level of the at least one selective A1 adenosine antagonist on a concentration of 10-500 ng/ml. The amount of the at least one selective A1 adenosine antagonist to be administered to reach and maintain a specific plasma level of the at least one selective A1 adenosine antagonist correspond to specific dosages to be administered to a patient. The skilled artisan is able to select an appropriate dosage for a specific patient. The invention also pertains to any arbitrary concentration or concentration range, which lie within the range of 10-500 ng/ml. In a preferred embodiment, the at least one selective adenosine A1 antagonist has a concentration of 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, and 500 ng/ml, and any arbitrary concentration or concentration range, which lie in any ranges defined by two of the before mentioned concentration values, where the lower limit of said range is defined by the minor value and the upper limit of said range by the upper value, e.g. a range of 10-180 ng/ml, 320-390 ng/ml, 100-150 ng/ml, etc.

The time period of application of the maintenance dosage of the at least one selective A1 adenosine antagonist lies between 0.1-48 hours to maintain the plasma level of the at least one selective A1 adenosine on a concentration of 10-500 ng/ml. The invention further pertains to a period of any arbitrary time interval which lies within time period of 0.1-48 hours. In a preferred embodiment, the time period of administration of the maintenance dosage is 0.1, 0.3, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20, 20.5, 21, 21.5, 22, 22.5, 23, 23.5, 24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29, 29.5, 30, 30.5, 31, 31.5, 32, 32.5, 33, 33.5, 34, 34.5, 35, 35.5, 36, 36.5, 37, 37.5, 38, 38.5, 39, 39.5, 40, 40.5, 41, 41.5, 42, 42.5, 43, 43.5, 44, 44.5, 45, 45.5, 46, 46.5, 47, 47.5 and 48 hours, and any arbitrary period which lies in any ranges defined by two of the before mentioned hour values, where the lower limit of said range is defined by the minor value and the upper limit of said range by the upper value, e.g. a range of 1-2 hours, 0.1-10 hours, 0.2-6 hours, 2-45 hours, 9.5-35 hours, etc.
The at least one selective adenosine A1 receptor antagonist may be administered intravenously in a loading dosage followed by a maintenance dosage, and the amount of the at least one selective adenosine A1 receptor antagonist loading dosage is administered at a time period of 5-25 minutes, prior to the administration of said at least one radiocontrast media, and the maintenance dosage of the at least one selective adenosine A1 receptor antagonist is administered over a period of up to 48 hours subsequent to administration of the loading dosage of said at least one selective A1 receptor antagonist, in a preferred embodiment over a period of up to 0.1, 0.3, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20, 20.5, 21, 21.5, 22, 22.5, 23, 23.5, 24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29, 29.5, 30, 30.5, 31, 31.5, 32, 32.5, 33, 33.5, 34, 34.5, 35, 35.5, 36, 36.5, 37, 37.5, 38, 38.5, 39, 39.5, 40, 40.5, 41, 41.5, 42, 42.5, 43, 43.5, 44, 44.5, 45, 45.5, 46, 46.5, 47, 47.5 and 48 hours. The invention pertains to a period of any arbitrary time interval which lies within time period of 5-25 minutes prior to the administration of said at least one radiocontrast media, and the maintenance dosage of the at least one selective adenosine A1 receptor antagonist is administered over a period of up to 48 hours subsequent to administration of the loading dosage of said at least one selective A1 receptor antagonist, in a preferred embodiment over a period of up to 0.1, 0.3, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20, 20.5, 21, 21.5, 22, 22.5, 23, 23.5, 24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29, 29.5, 30, 30.5, 31, 31.5, 32, 32.5, 33, 33.5, 34, 34.5, 35, 35.5, 36, 36.5, 37, 37.5, 38, 38.5, 39, 39.5, 40, 40.5, 41, 41.5, 42, 42.5, 43, 43.5, 44, 44.5, 45, 45.5, 46, 46.5, 47, 47.5 and 48 hours. In a preferred embodiment the at least one selective adenosine A1 receptor antagonist may be administered intravenously at 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 25 minutes, and any arbitrary period which lies in any ranges defined by two of the before mentioned minute values, where the lower limit of said range is defined by the minor value and the upper limit of said range by the upper value, e.g. a range of 10-18 minutes, 20-25 minutes, 12-15 minutes, etc., prior to the administration of said at least one radiocontrast media, and the maintenance dosage of the at least one selective adenosine A1 receptor antagonist is administered over a period of up to 48 hours subsequent to administration of the loading dosage of said at least one selective A1 receptor antagonist, in a preferred embodiment over a period of up to 0.1, 0.3, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20, 20.5, 21, 21.5, 22, 22.5, 23, 23.5, 24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29, 29.5, 30, 30.5, 31, 31.5, 32, 32.5, 33, 33.5, 34, 34.5, 35, 35.5, 36, 36.5, 37, 37.5, 38, 38.5, 39, 39.5, 40, 40.5, 41, 41.5, 42, 42.5, 43, 43.5, 44, 44.5, 45, 45.5, 46, 46.5, 47, 47.5 and 48 hours.
35, 35.5, 36, 36.5, 37, 37.5, 38, 38.5, 39, 39.5, 40, 40.5, 41, 41.5, 42, 42.5, 43, 43.5, 44, 44.5, 45, 45.5, 46, 46.5, 47, 47.5 and 48 hours. The invention pertains thus to a use comprising the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist in a loading dosage to be administered intravenously followed by a maintenance dosage, and the amount of the at least one selective adenosine A1 receptor antagonist loading dosage to be administered at a time period of 5-25 minutes, preferably 10-20 minutes, more preferably of 13-17 minutes, more preferably 15 minutes prior to the administration of said at least one radiocontrast media, and comprising the maintenance dosage of the at least one selective adenosine A1 receptor antagonist to administered over a period of up to 48 hours subsequent to administration of the loading dosage of said at least one selective A1 receptor antagonist. The invention pertains thus further to a pharmaceutical combination comprising the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist in a loading dosage to be administered intravenously followed by a maintenance dosage, and the amount of the at least one selective adenosine A1 receptor antagonist loading dosage to be administered at a time period of 5-25 minutes, preferably 10-20 minutes, more preferably of 13-17 minutes, more preferably 15 minutes prior to the administration of said at least one radiocontrast media, and comprising the maintenance dosage of the at least one selective adenosine A1 receptor antagonist to administered over a period of up to 48 hours subsequent to administration of the loading dosage of said at least one selective A1 receptor antagonist. The invention pertains thus further to a kit comprising the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist in a loading dosage to be administered intravenously followed by a maintenance dosage, and the amount of the at least one selective adenosine A1 receptor antagonist loading dosage to be administered at a time period of 5-25 minutes, preferably 10-20 minutes, more preferably of 13-17 minutes, more preferably 15 minutes prior to the administration of said at least one radiocontrast media, and comprising the maintenance dosage of the at least one selective adenosine A1 receptor antagonist to administered over a period of up to 48 hours subsequent to administration of the loading dosage of said at least one selective A1 receptor antagonist.

This invention in its broad scope is not limited to specific dosage forms, carriers, excipients, or the like, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.
It must be noted that as used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a therapeutically effective agent" includes a single agent as well as two or more different agents in combination, and reference to "a carrier" includes mixtures of two or more carriers as well as a single carrier, and the like.

The terms "A1AR" "selective adenosine A1 antagonist" and "selective adenosine A1 receptor antagonist" are used interchangeably herein to refer to a chemical compound that induces a desired pharmacological, physiological effect.

The at least one selective adenosine A1 antagonist may be administered orally and/or intravenously. The invention thus pertains to the use comprising the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist to be administered orally, preferably in an extended release formulation, prior to the administration of at least one radiocontrast agent.

The invention thus pertains to the use comprising the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist in a loading dosage to be administered intravenously followed by a maintenance dosage, and the amount of the at least one selective adenosine A1 receptor antagonist loading dosage to be administered at a time period of 5-25 minutes, preferably 10-20 minutes, more preferably of 13-17 minutes, more preferably 15 minutes prior to the administration of said at least one radiocontrast media, and comprising the maintenance dosage of the at least one selective adenosine A1 receptor antagonist to administered over a period of up to 48 hours subsequent to administration of the loading dosage of said at least one selective A1 receptor antagonist.

The invention thus pertains to a pharmaceutical combination comprising the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist to be administered orally, preferably in an extended release formulation, prior to the administration of the at least one radiocontrast agent.

The invention thus pertains to a pharmaceutical combination comprising the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist in a loading dosage to be administered intravenously followed by a maintenance dosage, and the amount of
the at least one selective adenosine A1 receptor antagonist loading dosage to be administered at a time period of 5-25 minutes, preferably 10-20 minutes, more preferably of 13-17 minutes, more preferably 15 minutes prior to the administration of said at least one radiocontrast media, and comprising the maintenance dosage of the at least one selective adenosine A1 receptor antagonist to administered over a period of up to 48 hours subsequent to administration of the loading dosage of said at least one selective A1 receptor antagonist.

The invention thus pertains to a kit comprising the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist to be administered orally, preferably in an extended release formulation, prior to the administration of the at least one radiocontrast agent.

The invention thus pertains to a kit comprising the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist in a loading dosage to be administered intravenously followed by a maintenance dosage, and the amount of the at least one selective adenosine A1 receptor antagonist loading dosage to be administered at a time period of 5-25 minutes, preferably 10-20 minutes, more preferably of 13-17 minutes, more preferably 15 minutes prior to the administration of said at least one radiocontrast media, and comprising the maintenance dosage of the at least one selective adenosine A1 receptor antagonist to administered over a period of up to 48 hours subsequent to administration of the loading dosage of said at least one selective A1 receptor antagonist.

The term "intravenously" is pertaining to parenteral application, which includes injection or infusion into the vein and the artery, without limiting the group of parenteral application forms.

The term "orally" is relating to enteral application, which includes application of e.g. tablets, drops, pills, capsules, pellets, granules, etc. by mouth, without limiting the group of enteral application forms.

"Extended release" refers to a pharmaceutically dosage form. The term "extended" includes e.g. "prolonged", "retard", "retentive" and "delayed" dosage forms, without limiting.

The term "container" is referring to a hermetically sealed storage box for pharmaceuticals. It includes storage boxes for fluid pharmaceuticals as e.g. ampoules, vials, flask, dispensers,
syringes, etc. as well as storage boxes for solid pharmaceuticals as e.g. blisters, capsules, etc. without limiting the group of storage boxes.

The term "irreversible" as used herein can be used interchangeably with the term "permanent".

By "pharmaceutically acceptable" such as in the recitation of a "pharmaceutically acceptable carrier", a "pharmaceutically acceptable auxiliary" or a "pharmaceutically acceptable salt" is meant herein a material that is not biologically or otherwise undesirable, i.e., the material may be incorporated into a pharmaceutical combination administered to a patient without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the combination in which it is contained. "Pharmacologically active", as in a "pharmacologically active" derivative or metabolite, refers to a derivative or metabolite having the same type of pharmacological activity as the parent compound and approximately equivalent in degree. When the term "pharmaceutically acceptable" is used to refer to a derivative of an active agent, it is to be understood that the compound is pharmacologically active as well, i.e., therapeutically effective for the treatment of radiocontrast media induced nephropathy.

"Carriers "or "pharmaceutically acceptable auxiliary" as used herein refer to conventional pharmaceutical acceptable excipient materials suitable for drug administration, and include any such materials known in the art that are nontoxic and do not interact with other components of a pharmaceutical combination or drug delivery system in a deleterious manner.

As used herein, the terms "comprising" and "including" are used herein in their open, non-limiting sense.

The term "prodrug" as used herein, represents derivatives of the compounds of the invention that are drug precursors which, following administration to a patient, release the drug in vivo via a chemical or physiological process. As used herein, the term "prodrug" includes metabolic precursors. In particular, pro-drugs are derivatives of the compounds of the invention in which functional groups carry additional constituents which may be cleaved under physiological conditions in vivo and thereby releasing the active principle of the compound (e.g., a prodrug on being brought to a physiological pH or through an enzyme action is converted to the desired drug form). Prodrugs are bioreversible derivatives of drug molecules used to overcome some barriers to the utility of the parent drug molecule. These barriers include, but are not limited to,
solubility, permeability, stability, presystemic metabolism and targeting limitations (Bundgaard, 1985[17]). Prodrugs, i.e. compounds that when administered to humans by any known route, are metabolised to compounds having formula I, belong to the invention.

The term "pharmacologically acceptable salts" refers to salt forms that are pharmacologically acceptable and substantially non-toxic to the subject being administered the compounds of the invention. Preferably the pharmacologically acceptable salts is a methanesulfonate salt.

The term "solvates" pertains to the association of suitable organic solvent molecules with molecules or ions of an A1AR. As used herein, the term "solvates" refers to stable solvates, containing a defined number of solvent molecules pro molecule of a compound of formula I, and inclusion complexes, which are less stable and contain a variable number of solvent molecules pro molecule of a A1AR.

The term "treatment" as used herein refers to reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, prevention of the occurrence of symptoms and/or their underlying cause, and improvement or remediation of damage. Thus, for example, "treatment" of a patient involves prevention of a particular disorder or adverse physiological event in a susceptible individual as well as treatment of a clinically symptomatic individual.

The “increase in serum creatinine level” induced by radiocontrast media might be transient, persistent or irreversible, preferably transient. Reference values for serum creatinine levels (see http://www.mnceus.com/renal/renalcreta.html[18]) in adult male lies approximately at 0.8 - 1.4 mg/dl, in adult female at 0.6 - 1.1 mg/dl, and in children at 0.2 - 1.0 mg/dl. An arbitrary range of values of between 25% - 50% or even higher increase in serum creatinine levels from reference values defines CIN. An increase of any arbitrary value within in the range of 25-70% in serum creatinine levels defines CIN. An “increase in serum creatinine level” as measurable physiological parameter defines a disease condition well understood by the skilled artisan. In a preferred embodiment, an increase of 25, 30, 35, 40, 45, 50, 55, 60, 65 and 70%, and any arbitrary range which lies in any ranges defined by two of the before mentioned values, where the lower limit of said range is defined by the minor value and the upper limit of said range by the upper value, e.g. a range of 25-30%, 25-35%, 30-60%, etc., defines CIN. This definition may in part account for the transient, persistent or irreversible elevations of serum creatinine levels.
The "decrease in renal blood flow" induced by radiocontrast media might be transient, persistent or irreversible, preferably transient. Reference value for blood flow in the kidney is approximately 20% of the cardiac output per minute, thus lies at 1000 ml/min in a healthy human. An arbitrary range of values of between 20% - 80% or even higher decrease in renal blood flow from reference value defines CIN. A decrease of any arbitrary value or value range within in the range of 20-80% in renal blood flow defines CIN. A "decrease in renal blood flow" as measurable haemodynamic parameter defines a disease condition well understood by the skilled artisan. In a preferred embodiment, a decrease of 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85 and 90%, and any arbitrary value or value range which lies in any ranges defined by two of the before mentioned values, where the lower limit of said range is defined by the minor value and the upper limit of said range by the upper value, e.g. a range of 25-30%, 20-35%, 30-60%, etc., defines CIN. This definition may in part account for the transient, persistant and irreversible depressions of renal blood flow values.

The renal blood flow can be measured using MRI (magnetic resonance imaging) techniques to determine renal blood flow and renal vascular resistance as well as PAH (para amino hipuric acid) infusion techniques.

Any of the described A1AR may be administered in the form of a salt, ester, amide, prodrug, active metabolite, analog, solvate or the like, provided that the salt, ester, amide, prodrug, active metabolite, analog, or solvate is pharmaceutically acceptable and pharmacologically active in the present context. Salts, esters, amides, prodrugs, metabolites, analogs, solvates and other derivatives of the active agents may be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry and described, for example, by J. March (1992)."
intravenous dosage forms are as described herein. Each dosage form may be individually housed. The present kits will also typically include means for packaging the individual kit components, i.e., the dosage forms, the container means, and the written instructions for use.

It is preferred that the therapeutically effective amount of A1AR is administered in a form, as emphasized above. However, in some cases, a patient may be given each, the therapeutically effective amount of A1AR and the RM, in its own separate dosage form, or a combination of individual "combination" dosage forms containing two or more of the present therapeutically effective A1ARs. When separate dosage forms are used, the A1AR and the RM can be administered at essentially the same time (concurrently), or at separately staggered times (sequentially). Optimum beneficial effects are achieved when the active blood plasma level concentrations of the A1AR agent is maintained while administration of the RM. These optimal beneficial effects can be achieved by application of a loading dose following by a maintenance dose. The loading dose will increase the blood plasma level very fast while the maintenance dose will then keep the achieved plasma level. A form comprising all the A1AR and the RM is, however, much preferred. Such a dosage form provides convenience and simplicity for the patient, thus increasing the chances for patient compliance. Since two or even more active agents are being used together in combination, the potency of each of the agents and the interactive effects achieved by combining them together must also be taken into account. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective or prophylactic effective dosage amounts.

The term "alkyl" refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. The term alkyl further includes alkyl groups, which can further include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone, e.g., oxygen, nitrogen, sulfur or phosphorous atoms. In preferred embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C₁-C₃₀ for straight chain, C₃-C₃₀ for branched chain), and more preferably 20 or fewer, e.g. in an embodiment "alkyl" may be C₁-C₆ or in a further embodiment C₁-C₄. Likewise, in an embodiment cycloalkyls have from 4-10 carbon atoms in their ring structure, and in a further embodiment cycloalkyls have from 5-7 carbon atoms in their ring structure, e.g. 5, 6 or 7 carbons in the ring structure. Moreover, the term “optionally substituted alkyl” as used throughout the specification and claims is intended to include both "unsubstituted alkyls" and
"substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, arloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylaryl amino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amido, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclic, alkylaryl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. Cycloalkyls can be further substituted, e.g., with the substituents described above.

An "alkylaryl" moiety is an alkyl substituted with an aryl (e.g., phenylmethyl (benzyl)). The term "alkyl" also includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

The term "aryl" as used herein, refers to the radical of aryl groups, including 5and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, pyrrole, furan, thiophene, imidazole, benzoxazole, benzothiazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Aryl groups also include polycyclic fused aromatic groups such as naphthyl, quinolyl, indolyl, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "heterocyclic ring". The aromatic ring can be substituted at one or more ring positions with such substituents as described above, as for example, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, arloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylaryl amino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amido, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclic, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings which are not aromatic so as to form a polycycle (e.g., tetralin).
The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen, preferred heteroatom is nitrogen.

It will be noted that the structure of some of the compounds of this invention includes asymmetric carbon atoms. It is to be understood accordingly, that the isomers arising from such asymmetry (e.g., all enantiomers and diastereomers) are included within the scope of this invention, unless indicated otherwise. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemically controlled synthesis.

The selective adenosine A1 antagonists described in the present invention have low lipophilic properties and therewith high hydrophilic properties resulting in good water solubility. The significantly lower lipophilic properties of the compounds used in the present invention distinguish said compounds over other known selective A1 antagonists; exemplary data is depicted in the table below (Table 1: lipophilic properties of selective adenosine A1 antagonists.)

<table>
<thead>
<tr>
<th>Substance</th>
<th>PGP-factor</th>
<th>Permeability (%)</th>
<th>LogP (ACD v9.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance 1</td>
<td>1.5</td>
<td>37.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Substance 2</td>
<td>10.1</td>
<td>27.0</td>
<td>-1.4</td>
</tr>
<tr>
<td>KW3902</td>
<td>1.4</td>
<td>31.1</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Table 1: lipophilic properties of selective adenosine A1 antagonists

From the receptor binding and enzyme profiling of substance 1 in a wide range of assay, it was concluded that substance 1 behaved as a selective adenosine A1 receptor ligand with some phosphodiesterase PDE4 inhibiting activity. The displacement of rolipram by substance 1 from phosphodiesterase PDE4 sites correlated with the relatively potency of substance 1 to inhibit this enzyme; the calculated $pK_i$ of the PDE4 inhibition was 750nM; the activities on other phosphodiesterases (PDE 1, 2, 3, 5 and 6) were at least 25 fold lower. The phosphodiesterase PDE4 inhibiting activity may be used for titration purposes of patients. The phosphodiesterase PDE4 inhibiting activity of the compounds used in the present invention prevents overdosage of the selective A1 antagonist by alarming the patients with self-evident, non-serious signals like e.g. headache before serious events like e.g. CNS convulsion can occur.
EXPERIMENTAL

1. Effects of acute application of substance 1 on diuresis and natriuresis following radiocontrast media (diatrizoate) in anesthetized rats

The radiocontrast media-dependent acute kidney failure was induced using an experimental protocol based on that published by the group of Osswald. Male Sprague-Dawley rats of approximately 300 g body weight were acclimatized for at least 1 week before the start of the chronic pretreatment with the nitric oxide synthase inhibitor N-nitro-L-arginine methyl ester (L-NAME for 7-9 weeks at a daily dose of 5 mg/kg). For the experiments, the overnight fasted rats (which had continued free access to drinking water) were anesthetized with Inactin (80 mg/kg, given i.p. as a bolus). Catheters were placed (i) in the trachea, (ii) in one jugular vein (for radiocontrast medium administration, and background saline infusion; see below), (iii) in the other jugular vein for vehicle or substance 1 administration, (iv) in the carotid artery for blood sampling, and part of the background saline infusion; see below), and (v) in the bladder for urine collection. The rats were kept on a heated table to maintain their body temperature at 37 °C. After collecting urine samples for 60-90 min for baseline measurements, the animals received vehicle or substance 1 as follows: a loading bolus of 0.15, or 1.5 mg substance 1 per kg, or vehicle, in a volume of 1 mL/kg, was applied intravenously, followed by a continuous intravenous infusion at a rate of 1.5, and 15 μg substance 1 per kg per min, or vehicle, in a volume of 11 μL/kg.min until the end of the experiment. With these dose regimens steady-state plasma levels of substance 1 were 59 ± 23, and 314 ± 36 ng/mL, respectively. 10 min after the start of the substance 1 (or vehicle) treatment, diatrizoate (meglumine salt, Urolux , 0.61 g diatrizoate/mL, corresponding to a total iodine content of 290 mg/mL, Sanochemia Diagnostics, Neuss, Germany), prewarmed at body temperature, was infused iv over 3 min at a dose of 2.55 mL/kg, corresponding to 740 mg iodine/kg (the timepoint of contrast medium administration was defined as t₀). A background saline solution was infused right from the beginning and maintained at a rate of ~1.2 mL/h per 100 g until the end of the experiments (0.24 mL/h via the arterial cathether, and 0.96 mL/h via the venous line). This infusion was required to compensate for the volume loss due to the operation, and the subsequent blood sampling, but also to insure the patency of the arterial catheter between the blood sampling timepoints. Urine samples were collected according to the following schedule: baseline (60-90 min preceding the start of substance 1, or vehicle, administration), t₀ – 30 min (0.5 h timepoint), 30 – 60 min (1 h timepoint), 60 – 120 min (2 h timepoint), and 120 – 180 min (3 h timepoint). Plasma samples were taken at the end of
each of the above periods. The measured values of urine volume, and urine levels of Na\(^+\) were used to calculate the rates of diuresis and natriuresis over the time intervals mentioned above. Substance 1 treatment produced a large and significant increase in urine production in the first 30 min following contrast medium administration, as compared to the vehicle control group; in spite of the fact that the rate of diuresis then returned towards lower values in all groups, a stimulating effect of substance 1 persisted for at least 3 h. Because radiocontrast media are eliminated via the urine, this diuretic effect of substance 1 is likely to strongly promote their elimination and thus to limit their toxicity.

<table>
<thead>
<tr>
<th>Time after CM</th>
<th>Vehicle control</th>
<th>Substance 1 Low dose</th>
<th>P vs. vehicle</th>
<th>Substance 1 high dose</th>
<th>P vs. vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 h</td>
<td>17.10 ± 1.42</td>
<td>27.31 ± 2.36</td>
<td>***</td>
<td>28.01 ± 2.02</td>
<td>***</td>
</tr>
<tr>
<td>1 h</td>
<td>3.76 ± 0.31</td>
<td>3.87 ± 0.40</td>
<td>n.s.</td>
<td>4.97 ± 0.30</td>
<td>n.s.</td>
</tr>
<tr>
<td>2 h</td>
<td>1.96 ± 0.15</td>
<td>3.34 ± 0.42</td>
<td>**</td>
<td>3.13 ± 0.27</td>
<td>**</td>
</tr>
<tr>
<td>3 h</td>
<td>2.14 ± 0.40</td>
<td>3.54 ± 0.50</td>
<td>n.s.</td>
<td>3.11 ± 0.36</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Table 2: Effects of substance 1 on diuresis following diatrizoate administration in anesthetized in rats, Values are expressed in mL per kg body weight per h, and represent means ± SEM (n = 14 – 24). Statistical significance was evaluated using one-way analysis of variance followed by a Bonferroni test. n.s.: non significant; *: P < 0.05; **: P < 0.01; and ***: P < 0.001 vs. vehicle controls.

Likewise, substance 1 caused a pronounced and sustained increase in sodium excretion over values seen in the vehicle control group. Chloride excretion was stimulated by substance 1 in a similar way, whereas potassium excretion was not relevantly affected by the compound throughout the experiment (not shown).

<table>
<thead>
<tr>
<th>Time after CM</th>
<th>Vehicle control</th>
<th>Substance 1 Low dose</th>
<th>P vs. vehicle</th>
<th>Substance 1 high dose</th>
<th>P vs. vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 h</td>
<td>1332 ± 184</td>
<td>3039 ± 354</td>
<td>***</td>
<td>3301 ± 306</td>
<td>***</td>
</tr>
<tr>
<td>1 h</td>
<td>185 ± 39</td>
<td>338 ± 81</td>
<td>n.s.</td>
<td>520 ± 77</td>
<td>**</td>
</tr>
<tr>
<td>2 h</td>
<td>153 ± 40</td>
<td>613 ± 121</td>
<td>**</td>
<td>591 ± 88</td>
<td>**</td>
</tr>
<tr>
<td>3 h</td>
<td>329 ± 72</td>
<td>842 ± 121</td>
<td>**</td>
<td>830 ± 91</td>
<td>**</td>
</tr>
</tbody>
</table>
Table 3: Effects of substance 1 on sodium excretion following diatrizoate administration in anesthetized in rats. Values are expressed in μmol per kg body weight per h, and represent means ± SEM (n = 14 – 24). Statistical significance was evaluated using one-way analysis of variance followed by a Bonferroni test. n.s.: non significant; *: P < 0.05; **: P < 0.01; and ***: P < 0.001 vs. vehicle controls.

2. Effects of acute application of substance 1 on renal blood flow and oxygenation following radiocontrast media (iodixanol) in anesthetized rats

The experimental protocol was based on a previously published methodology. The experiments were performed using adult male 3-4 months old Wistar rats. Body weight ranged from 250 to 400 g. The rats received a standard chow diet. Feeding and drinking was discontinued approx. 12 hours before the surgery. The animals were anesthetized by intraperitoneal injection of urethane solution (2% in water; 6 ml per kg), and placed on a heated table to maintain body temperature at 37°C throughout surgery and subsequent experiments. After an incision in the left groin the femoral artery was carefully prepared and cannulated to measure the mean arterial blood pressure. Another catheter was placed into the carotid artery for administration of contrast medium. Finally, an inflatable cuff was placed around the abdominal aorta above the origin of the renal arteries. A servo controlled inflation of the cuff allowed to reduce and maintain renal perfusion pressure at a preset level. Two 500μm diameter optical fibers were implanted into the cortex and the outer medulla of left kidney, to determine local laser-Doppler fluxes, and an ultrasound transit time flowprobe was placed around the renal artery of the same kidney to determine total kidney blood flow (RBF). Renal oxygen levels (oxygen partial pressure = pO₂) was likewise determined locally (cortical and medullary pO₂, respectively; OxyLite, Oxford Optronics). After implantation and stabilization, the experiment was started by measuring hemodynamic and oxygenation parameters under baseline conditions. Vehicle or substance 1 (5 mg/kg as an intravenous bolus) were then administered. New measurements were performed, and 30 min after vehicle or substance 1 administration, iodixanol (Visipaque 320; 1.5 mL i.a.; Amersham Buchler, Braunschweig, Germany), or vehicle was applied. After another 20 min, measurements were repeated (over a period of 20 min, shown in figures below). The experimental groups were thus: 1. Vehicle + Vehicle ('control'), Vehicle + Visipaque, and substance 1 + Visipaque.

Substance 1 did not modify hemodynamic parameters (arterial blood pressure, RBF) before the Visipaque challenge (not shown). Following Visipaque administration, a strong, transient
increase in mean arterial blood pressure was observed (by ~ 35 mm Hg), which lasted for approximately 10 min, and was partially prevented by substance 1 (not shown). In the Vehicle + Visipaque group, renal cortical blood flow showed a short initial increase which was followed by a progressive and significant decrease, as compared to the vehicle control group (Figure 3). In contrast, in the presence of substance 1, cortical blood flow displayed a sustained and significant increase, blood flow remaining significantly elevated until the end of the measurement period as compared to the Vehicle + Visipaque group (Figure 3). Cortical vascular conductance was rapidly and stably lowered by Visipaque, whereas substance 1 maintained this parameter at levels seen in the vehicle control group (Figure 4). Similarly, medullary blood flow transiently rose (for ~ 3 min) after Visipaque injection, and then fell below control levels; concomitantly, medullary vascular conductance was rapidly and stably depressed by Visipaque; substance 1 treatment only partially (but significantly) prevented these effects (not shown). Finally, substance 1 caused a significant increase in cortical pO₂ which persisted until the end of the experiment (Figure 5).

Overall, these observations show that substance 1 improves renal hemodynamics and oxygenation, thus at least partially antagonizing the potentially deleterious effects of the radiocontrast medium iodixanol.

STUDY PROTOCOL

Study 1
Animal studies are performed in 60 anesthetized rats. Renal hemodynamics are assessed, and oxygen tension within the kidney is measured after application of RM. Total blood flow to the kidney is quantified by the transit time method, local hemodynamics by laser-Doppler Flux. In addition, regional oxygen tension of the kidney is assessed and urine is collected to determine urine osmolality, viscosity and diuresis. Using a recently established technique (Wronski, 2003²¹), it is possibly to assess the TGF response in this setting. The RM significantly reduces renal blood flow and perturbs regional kidney oxygenation. This effect is most likely due to viscous properties, as seen by an increase in urine viscosity. These RM effects on renal hemodynamics (renal blood flow and hypoxia) are alleviated or even reversed by prior administration of the A1AR antagonists.

Two protocols are made: Protocol 1: Fluid restriction takes place 24 h before experiments. This leads to augmented concentration of RM in the tubular system. Catheters, transit-time
flowmeters, laser-Doppler probes and sounds for assessing absolute \( pO_2 \) are implanted. Control measurements are recorded, and then the RM is given. Protocol 2: Measures will then be repeated. In the fluid replete animal, urine volume, osmolarity and viscosity are determined. Control measurements are recorded, then, the RM is given.

Assessment of renal blood flow, oxygen tension and regional blood flows and the TGF response in rats after water restriction take place. Reduced plasma volume is a generally recognized risk factor, since CM is concentrated in the tubules during antidiuresis.

Figure 1 depicts the protocols. In the top panel, the RM is given after control measurements (N=15). The bottom panel dicls the series where the A1ARis given prior to the RM (N=15).

In order to collect sufficient urine, volume repleted rats are used. Diuresis, urine osmolality and viscosity are assessed for control and the RM (N=15, figure 2 top panel), and for control, the A1AR and the A1AR + the RM (N=15, figure 2 bottom panel). All experiments are performed on adult, male Wistar rats obtained from the animal facility of the institute. The rats are housed in groups. All animals are randomly distributed to the protocols. The animals are identified by cage number. A standard rat diet (Altromin 1324, Altromin GmbH, D-32791 Lage) serve as chow. Feeding and drinking is discontinued approx. 12 hours before the surgery for protocol 1. In protocol 2, drinking is allowed ad libitum. Drinking water is offered ad libitum, except for a time period of 12h before CM application. Thus, the animals are water deprived. In protocol 2, water is offered ad libitum until immediately before the experiment. Granulated textured wood (Granulat A2, J. Brandenburg, D-49424 Goldenstedt) is used as bedding material for the cages. The cages are changed and cleaned every day between 6:00 and 8:00 a.m. During the acclimatization, the animals are kept in groups of 3 - 5 animals in MAKROLOM cages each (type 4) at a room temperature of 22° C ± 3 ° C and a relative humidity of 60% ± 20%. Deviation might be caused for example during the cleaning procedures. Anesthesia is introduced and maintained by urethane. Rats are placed on a heated table to maintain body temperature at 37°C throughout the surgery. The body temperature is controlled during the study. After an incision in the left groin the femoral artery is carefully prepared and cannulated with a polypropylene catheter (PP 10) to measure the renal perfusion pressure (RPP). Another catheter (PP 50) of the same material is placed into the carotid artery to measure systemic blood pressure (BP) and heart rate (HR). Finally, an inflatable cuff is placed around the abdominal aorta; one above and the other below the origin of the renal arteries. A servo controlled inflation of the proximal cuff allowed it to reduce and maintain renal perfusion pressure at a preset level. Two 500µm diameter optical fibers (Moore instruments, GB)
are implanted into the cortex and the medulla of left kidney, and an ultrasound transit time
flowprobe (1RB, Transonic Systems inc, USA) is placed around the renal artery of the same
kidney to determine local blood flows (LFC and LFM respectively) and total kidney blood flow
(RBF). \( pO_2 \) is likewise locally determined. Local blood flow is measured and processed by a laser-
Doppler flowmeter (Moore Instruments, GB). The arterial catheter is connected to the calibrated
pressure transducer. The inflatable cuff is connected to an extracorporeal servo control system and
the flow probes are connected via extension cables to the Flowmeters. Oxygen partial pressure
sensing probes are positioned in a corresponding manner. After analog to digital conversion all
data (BP, RPP, RBF, LFC, LFM, local oxygen tension) are stored on-line in ASCII format by a
computer system (IBM compatible AT). After implantation and stabilization, the experiment is
started. The test solutions are infused. After 5 min equilibrium, measurements of RBF, local fluxes
and local \( pO_2 \) is commenced. Then, a 5 min step response is obtained to assess TGF. Urine is
collected 35 min to evaluate diuresis, osmolality and viscosity. When required, modifications are
made to the protocols. Total and regional RBF and oxygen tension in the renal medulla and cortex
are assessed according to prior studies (Flemming, 2000 and 2001\textsuperscript{22}) by measuring laser-Doppler-
fluxes and direct assessment of \( pO_2 \). After the calculation of individual mean values of every
parameter, these mean values of every animal are used to calculate group averages and standard
errors of each control/intervention group. The latter are used to test differences for statistical
significance, preferably levels of less than 0.05 are considered to indicate significance. The used
test methods are chosen with respect to the parameters of the underlying data.

Study 2
A study analogous to the one described by Yao (2000\textsuperscript{10}) with selected variations in the protocol
is performed. In contrast to the Yao study, chronic as well as acute experiments are carried out.
Indometacine is used in addition to L-name (N-\( \varepsilon \)-nitro-L-arginine methyl ester) in this study.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: In volume restricted rats, hemodynamic measurements are made, and the TGF
response is assessed.

Figure 2: Experimental setting 2 is used for collecting urine. Diuresis, urine osmolality and urine
viscosity are determined.

Figure 3: Effects of Visipaque and substance 1 on renal cortical blood flow, Measurements over
20 min period following injection of Visipaque or vehicle (control) at time 0. Shown are means ±
SEM (n = 9), expressed as relative values compared to cortical flow rates recorded before Visipaque (or vehicle) challenge. *: P < 0.05 Visipaque vs. Control; +: P < 0.05 substance 1+Visipaque vs. Visipaque.

Figure 4: Effects of Visipaque and substance 1 on renal cortical vascular conductance, Measurements over 20 min period following injection of Visipaque or vehicle (control) at time 0. Shown are means ± SEM (n = 9), expressed as relative values compared to cortical flow rates recorded before Visipaque (or vehicle) challenge. *: P < 0.05 Visipaque vs. Control; +: P < 0.05 substance 1+Visipaque vs. Visipaque.

Figure 5: Effects of Visipaque and substance 1 on renal cortical oxygenation (pO₂), Measurements over 20 min period following injection of Visipaque or vehicle (control) at time 0. Shown are means ± SEM (n = 9), expressed as relative values compared to cortical flow rates recorded before Visipaque (or vehicle) challenge. *: P < 0.05 Visipaque vs. Control; +: P < 0.05 substance 1+Visipaque vs. Visipaque.

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8 Erley et al., "Adenosine antagonist theophylline prevents the reduction of glomerular filtration rate after contrast media application", Kidney Int. (1994), 45, 1425-31
9 K. Akawara et al., "Role of adenosine in the renal responses to contrast medium", Kidney Int. (1996), 49(5), 1199-206
11 Greiner, Dissertation “Prophylaxis of Contrast Induced Nephropathy with Theophylline and Acetylcysteine in ICU-Patients”, TU München, 19.10.2005
13 EP 1 386 609, filed by CV Therapeutics
14 WO 99/31101, filed by Univ. South Florida
15 WO 99/62518, WO 01/39777, WO 02/057267, all filed by Osi Pharmaceuticals and WO 2004/094428 filed by Solvay Pharmaceuticals
Claims

1. A use of a therapeutically effective amount of at least one selective adenosine A1 antagonist of formula I

![Chemical Structure](image)

wherein

R1 and R2 are each independently selected from a hydrogen atom, an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety or together form an optionally substituted heterocyclic ring;

R3 is selected from a hydrogen atom or an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety;

R4 and R5 are each independently selected from a halogen atom, a hydrogen atom or an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety, or R4 and R5 together form an optionally substituted heterocyclic or optionally substituted carbocyclic ring;

and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof,

for the manufacture of a medicament for the prevention of nephropathy induced by at least one radiocontrast media, in mammals or humans.

2. A use of a therapeutically effective amount of at least one selective adenosine A1 antagonist of formula I

![Chemical Structure](image)
as defined in claim 1,
and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof,
for the manufacture of a medicament for the prevention of increase in serum creatinine levels induced by at least one radiocontrast media, preferably of a transient, persistent or irreversible increase in serum creatinine levels induced by radiocontrast media, in mammals or humans.

3. A use of a therapeutically effective amount of at least one selective adenosine A1 antagonist of formula I

\[
\text{R1} - \text{N} - \text{R2} \quad \text{R5} \\
\text{R3} - \text{N} - \text{N} - \text{R4} \\
\text{I}
\]

as defined in claim 1,
and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof,
for the manufacture of a medicament for the prevention of decrease in renal blood flow induced by at least one radiocontrast media, preferably of a transient, persistent or irreversible decrease in renal blood flow induced by radiocontrast media, in mammals or humans.

4. A use of a therapeutically effective amount of at least one selective adenosine A1 antagonist of formula I

\[
\text{R1} - \text{N} - \text{R2} \quad \text{R5} \\
\text{R3} - \text{N} - \text{N} - \text{R4} \\
\text{I}
\]
as defined in claim 1,
and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof,
for the manufacture of a medicament for the prevention of a risk or need of dialysis in a human or mammalian patient, preferably of transient, persistent or irreversible dialysis, said patient being subject to receive radiocontrast media.

5. A use according to any of claims 1, 2, 3 or 4, wherein the time period of application of the therapeutically active amount of said at least one selective A1 adenosine antagonist is sufficient to maintain the plasma level of the at least one selective A1 adenosine on a concentration of 10-500 ng/ml, preferably 20-400 ng/ml, more preferably 30-300 ng/ml.

6. A use according to any of claims 1, 2, 3, 4 or 5, comprising the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist in a loading dosage to be administered intravenously and comprising a maintenance dosage, and the amount of the at least one selective adenosine A1 receptor antagonist loading dosage to be administered at a time period of 5-25 minutes, preferably 10-20 minutes, more preferably of 13-17 minutes, more preferably 15 minutes prior to the administration of said at least one radiocontrast media, and comprising the maintenance dosage of the at least one selective adenosine A1 receptor antagonist to be administered over a period of up to 48 hours subsequent to administration of the loading dosage of said at least one selective A1 receptor antagonist.

7. A use according to any of claims 1, 2, 3, 4 or 5, comprising the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist in an orally, preferably in an extended release formulation, to be administered prior to the administration of the at least one radiocontrast agent.

8. A use according to any of claims 1, 2, 3, 4, 5, 6 or 7, comprising the at least one radiocontrast media to be not earlier administered until the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist is sufficient to provide a plasma level concentration of 10-500 ng/ml, preferably 20-400 ng/ml, more preferably 30-300 ng/ml.
9. A use according to any of claims 1, 2, 3, 4, 5, 6, 7 or 8, comprising a time period of application of the maintenance dosage of a therapeutically effective amount of said at least one selective A1 adenosine antagonist to be sufficient to maintain the plasma level of the at least one selective A1 adenosine on a concentration of 10-500 ng/ml, preferably 20-400 ng/ml, more preferably 30-300 ng/ml.

10. A use according to any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9, wherein the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist is selected from pyrrolo[2,3-d]pyrimidine derivatives of formula I, as defined in claim 1, and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof.

11. A use according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, wherein the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist is selected from 4-[(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-trans-cyclohexanol methanesulfonate or (4S)-4-hydroxy-1-(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-L-prolinamide methanesulfonate, and/or a prodrug, and/or a solvate thereof.

12. A use according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11, wherein said at least one radiocontrast media is an iodinated or gadolinium-based radiocontrast media selected from the group consisting of bunaidid, biligram, bilimiro, bilopaque, cholinil, ethiodol, diatrat, dionosil, faignost, gadobutrol, gadodiamide, gadopentetate dimeglumine, gastrografin, hexabrix, hippodin, mangafodipir, amidotrizoate, ethiodized oil, imagopaque, iodamide, iopamidol, iodixanol, iodophene, iophendylate, isomer, iomepr, iopamidol, iopanoic acid, iopiperidol, iophendylate, iopromide, iopydol, ioximenol, iothalamic acid, iotrolan, ioversol, ioxilan, ioxaglic acid, isopaque, ipodate, meglumine iothalamate, meglumine acetrizoate, meglumine diatrizoate, metrizamide, myelotраст, omnipaque, osbil, optiray, optojod, opaconor, perflutren, phenobutidil, phentetiothalein sodium, priodax, propyldone, skiodan, sodium iodomethamate, sodium diatrizoate, telepaque, teridax, tetrabrom, thorotраст, triognost, 1,3,5-Tri-n-hexyl-2,4,6-triiodobenzene, tyro-
panoate, visipaque or xenetix, and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof.

13. A use according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12, wherein the medicament is a fixed combination.

14. A pharmaceutical combination comprising
   a) a therapeutically effective amount of at least one selective adenosine A1 antagonist, and
   b) at least one radiocontrast media,
   wherein the pharmaceutical combination being suitable for simultaneous, separate or step-wise administration to humans or mammals.

15. A pharmaceutical combination according to claim 14, comprising a therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist to be administered intravenously in a loading dosage and comprising a maintenance dosage, and the amount of the at least one selective adenosine A1 receptor antagonist loading dosage to be administered at a time period of 5-25 minutes, preferably 10-20 minutes, more preferably of 13-17 minutes, more preferably 15 minutes prior to the administration of said at least one radiocontrast media, and comprising the maintenance dosage of the at least one selective adenosine A1 receptor antagonist to be administered over a period of up to 48 hours subsequent to administration of the loading dosage of said at least one selective A1 receptor antagonist.

16. A pharmaceutical combination according to claim 14, comprising the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist in an orally, preferably in an extended release formulation, to be administered prior to the administration of the at least one radiocontrast agent.

17. A pharmaceutical combination according to any of claims 14, 15 or 16, comprising the at least one radiocontrast media to be not earlier administered until the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist is sufficient to provide a plasma level of a concentration of 10-500 ng/ml, preferably 20-400 ng/ml, more preferably 30-300 ng/ml.
18. A pharmaceutical combination according to any of claims 14, 15, 16 or 17, wherein the time period of application of the at least one selective A1 adenosine antagonist is sufficient to maintain the plasma level of the at least one selective A1 adenosine antagonist on a concentration of 10-500 ng/ml, preferably 20-400 ng/ml, more preferably 30-300 ng/ml.

19. A pharmaceutical combination according to any of claims 14, 15, 16, 17 or 18, wherein the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist is selected from pyrrolo[2,3d]pyrimidine derivatives of formula I

![](image)

wherein

R1 and R2 are each independently selected from a hydrogen atom, an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety or together form an optionally substituted heterocyclic ring;

R3 is selected from a hydrogen atom or an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety;

R4 and R5 are each independently selected from a halogen atom, a hydrogen atom or an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety, or R4 and R5 together form an optionally substituted heterocyclic or optionally substituted carbocyclic ring;

and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof.

20. A pharmaceutical combination according to any of claims 14, 15, 16, 17, 18 or 19, wherein the therapeutically effective amount of said at least one selective A1 adenosine receptor antagonist is selected from pyrrolo[2,3d]pyrimidine derivatives of formula I
wherein
R1 and R2 are each independently selected from a hydrogen atom, an optionally substituted alkyl or together form an optionally substituted heterocyclic ring;
R3 is a hydrogen atom or an optionally substituted aryl;
R4 and R5 are each independently selected from a halogen atom or a hydrogen atom;
preferably wherein
R1 is a hydrogen and R2 is an optionally substituted cyclohexyl ring, or R1 and R2 together form an optionally substituted pyrrolidine ring;
R3 is a phenyl ring;
R4 and R5 are each a hydrogen atom;
and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof.

21. A pharmaceutical combination according to any of claims 14, 15, 16, 17, 18, 19 or 20, wherein the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist is selected from 4-[(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-trans-cyclohexanol methanesulfonate or (4S)-4-hydroxy-1-(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-L-prolinamide methanesulfonate, and/or a prodrug, and/or a solvate thereof.

22. A pharmaceutical combination according to any of claims 14, 15, 16, 17, 18, 19, 20 or 21, wherein said at least one radiocontrast media is an iodinated or gadolinium-based radiocontrast media selected from the group consisting of bunaïod, biligram, bitimiro, bilopaque, cholimil, ethiodol, diatраст, dionosil, fatignost, gadobutrol, gadodiamide, gadopentetate dimeglumine, gastrografin, hexabrix, hippocin, mangafodipir, amidotrizoate, ethiodized oil, imagopaque, iodamide, iodipamide, iodixanol, iodophene, iophendylate, iomeron, iomeprrol, iopamidol, iopanoic acid, iopiperidol, iophendylate, iopromide, iopydol, iosimenol, iothalamic acid, iotrolan, ioversol, ioxilan,ioxaglic acid, isopaque, ipodate, meglumine iothalamate, meglumine acetrizoate, meglumine diatrizoate, metrizamide, myelotrat, omnipaque, osbıl, optiray, optojod, opacoron, perflutren, phenobutilodil, phentetiothalein sodium, priodax, propylidone, skiodan, sodium iodomethamate, sodium diatrizoate, telepaque, teridax, tetrabrom, thorotrast, triognost, 1,3,5-Tri-n-hexyl-
2,4,6-triodobenzene, tyropanoate, visipaque or xenetix, and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof.

23. A kit comprising
   a) a therapeutically effective amount of at least one selective adenosine A1 antagonist, and
   b) at least one radiocontrast media.
   wherein the pharmaceutical combination being suitable for simultaneous, separate or step-wise administration to humans or mammals.

24. A kit according to claim 23, comprising
   a) a loading dosage container of the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist to be administered intravenously
   b) a maintenance dosage container of the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist to be administered intravenously
   c) at least one radiocontrast media
   comprising the at least one selective adenosine A1 receptor antagonist to be administered intravenously in a loading dosage and comprising a maintenance dosage, and the amount of the at least one selective adenosine A1 receptor antagonist loading dosage to be administered at a time period of 5-25 minutes, preferably 10-20 minutes, more preferably of 13-17 minutes, more preferably 15 minutes prior to the administration of said at least one radiocontrast media, and comprising the maintenance dosage of the at least one selective adenosine A1 receptor antagonist to be administered over a period of up to 48 hours subsequent to administration of the loading dosage of said at least one selective A1 receptor antagonist.

25. A kit according to claim 23 comprising
   a) a container with the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist to be administered orally
   b) at least one radiocontrast media
comprising the at least one selective adenosine A1 receptor antagonist in an orally, preferably in an extended release formulation, to be administered prior to the administration of the at least one radiocontrast agent.

26. A kit according to any of claims 23, 24 or 25 comprising the therapeutically effective amount of said at least one radiocontrast media to be not earlier administered until the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist is sufficient to provide a plasma level of a concentration of 10-500 ng/ml, preferably 20-400 ng/ml, more preferably 30-300 ng/ml.

27. A kit according to any of claims 23, 24, 25 or 26, wherein the time period of application of the therapeutically effective amount of said at least one selective A1 adenosine antagonist is sufficient to maintain the plasma level of the at least one selective A1 adenosine on a concentration of 10-500 ng/ml, preferably 20-400 ng/ml, more preferably 30-300 ng/ml.

28. A kit according to any of claims 23, 24, 25, 26 or 27, wherein the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist is selected from pyrrolo[2,3-d]pyrimidine derivatives of formula I

\[
\text{I}
\]

wherein
R1 and R2 are each independently selected from a hydrogen atom, an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylary moiety or together form an optionally substituted heterocyclic ring;
R3 is selected from a hydrogen atom or an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylary moiety;
R4 and R5 are each independently selected from a halogen atom, a hydrogen atom or an optionally substituted alkyl, optionally substituted aryl, or optionally...
substituted alkylaryl moiety, or R4 and R5 together form an optionally substituted heterocyclic or optionally substituted carbocyclic ring; and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof.

29. A kit according to any of claims 23, 24, 25, 26, 27 or 28, wherein the therapeutically effective amount of said at least one selective A1 adenosine receptor antagonist is selected from pyrrolo[2,3-d]pyrimidine derivatives of formula I wherein

R1 and R2 are each independently selected from a hydrogen atom, an optionally substituted alkyl or together form an optionally substituted heterocyclic ring;

R3 is a hydrogen atom or an optionally substituted aryl;

R4 and R5 are each independently selected from a halogen atom or a hydrogen atom;

preferably wherein

R1 is a hydrogen and R2 is an optionally substituted cyclohexyl ring, or R1 and R2 together form an optionally substituted pyrrolidine ring;

R3 is a phenyl ring;

R4 and R5 are each a hydrogen atom;

and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof.

30. A kit according to any of claims 23, 24, 25, 26, 27, 28 or 29, wherein the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist is selected from 4-[(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-trans-cyclohexanol methanesulfonate or (4S)-4-hydroxy-1-(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-L-prolinamide methanesulfonate, and/or a prodrug, and/or a solvate thereof.

31. A kit according to any of claims 23, 24, 25, 26, 27, 28, 29 or 30, wherein said at least one radiocontrast media is an iodinated or gadolinium-based radiocontrast media selected from the group consisting of bunaiod, biligram, bilimiro, bilopaque, cholimil, ethiodol, diatраст, disosil, fatignost, gadobutrol, gadodiamide, gadopen-tetate dimeglumine, gastrografin, hexabrix, hippodin, mangaofidipir, amidotrizoate, ethiodized oil, imagopaque, iodamide, iodipamide, iodixanol, iodophene, io-
phenylate, iomer, iomeprol, iopamidol, iopanoic acid, iopiperidol, iophendylate, iopromide, iopydol, iosimenol, iothalamic acid, iotrolan, ioversol, ioxilan, ioxaglic acid, isopaque, ipodate, meglumine iothalamate, meglumine acetrizoate, meglumine diatrizoate, metrizamide, myelotrast, omnipaque, osbil, optiray, optojod, opacoron, perflutren, phenobutiodil, phentetiothalein sodium, priodax, propylidone, skiodan, sodium iodomethamate, sodium diatrizoate, telepaque, teridax, tetrabrom, thorotrast, triognost, 1,3,5-Tri-n-hexyl-2,4,6-triiodobenzene, tyrophanoate, visipaque or xenetix, and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof.
AMENDED CLAIMS
received by the International Bureau on 14 November 2007 (14.11.2007)

1. A use of a therapeutically effective amount of at least one selective adenosine A1 antagonist of formula I

\[
\text{Formula I}
\]

wherein
R1 and R2 are each independently selected from a hydrogen atom, an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety or together form an optionally substituted heterocyclic ring;
R3 is selected from a hydrogen atom or an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety;
R4 and R5 are each independently selected from a halogen atom, a hydrogen atom or an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety, or R4 and R5 together form an optionally substituted heterocyclic or optionally substituted carbocyclic ring;
and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof,
for the manufacture of a medicament for the prevention of nephropathy induced by at least one radiocontrast media, in mammals or humans.

2. A use of a therapeutically effective amount of at least one selective adenosine A1 antagonist of formula I

\[
\text{Formula I}
\]
as defined in claim 1,
and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof,
for the manufacture of a medicament for the prevention of increase in serum creatinine levels induced by at least one radiocontrast media, preferably of a transient, persistent or irreversible increase in serum creatinine levels induced by radiocontrast media, in mammals or humans.

3. A use of a therapeutically effective amount of at least one selective adenosine A1 antagonist of formula I

\[
\begin{align*}
\text{I} & \\
\text{R1} & \text{N} & \text{R2} \\
\text{N} & \text{N} & \\
\text{N} & \text{N} & \\
\text{R3} & \text{R4} & \\
\text{R5} & & \\
\end{align*}
\]

as defined in claim 1,
and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof,
for the manufacture of a medicament for the prevention of decrease in renal blood flow induced by at least one radiocontrast media, preferably of a transient, persistent or irreversible decrease in renal blood flow induced by radiocontrast media, in mammals or humans.

4. A use of a therapeutically effective amount of at least one selective adenosine A1 antagonist of formula I

\[
\begin{align*}
\text{I} & \\
\text{R1} & \text{N} & \text{R2} \\
\text{N} & \text{N} & \\
\text{N} & \text{N} & \\
\text{R3} & \text{R4} & \\
\text{R5} & & \\
\end{align*}
\]
as defined in claim 1,
and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof,
for the manufacture of a medicament for the prevention of a risk or need of dialysis in a human or mammalian patient, preferably of transient, persistent or irreversible dialysis, said patient being subject to receive radiocontrast media.

5. A use according to any of claims 1, 2, 3 or 4, wherein the time period of application of the therapeutically active amount of said at least one selective A1 adenosine antagonist is sufficient to maintain the plasma level of the at least one selective A1 adenosine on a concentration of 10-500 ng/ml, preferably 20-400 ng/ml, more preferably 30-300 ng/ml.

6. A use according to any of claims 1, 2, 3, 4 or 5, comprising the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist in a loading dosage to be administered intravenously and comprising a maintenance dosage, and the amount of the at least one selective adenosine A1 receptor antagonist loading dosage to be administered at a time period of 5-25 minutes, preferably 10-20 minutes, more preferably of 13-17 minutes, more preferably 15 minutes prior to the administration of said at least one radiocontrast media, and comprising the maintenance dosage of the at least one selective adenosine A1 receptor antagonist to be administered over a period of up to 48 hours subsequent to administration of the loading dosage of said at least one selective A1 receptor antagonist.

7. A use according to any of claims 1, 2, 3, 4 or 5, comprising the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist in an orally, preferably in an extended release formulation, to be administered prior to the administration of the at least one radiocontrast agent.

8. A use according to any of claims 1, 2, 3, 4, 5, 6 or 7, comprising the at least one radiocontrast media to be not earlier administered until the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist is sufficient to provide a plasma level concentration of 10-500 ng/ml, preferably 20-400 ng/ml, more preferably 30-300 ng/ml.
9. A use according to any of claims 1, 2, 3, 4, 5, 6, 7 or 8, comprising a time period of application of the maintenance dosage of a therapeutically effective amount of said at least one selective A1 adenosine antagonist to be sufficient to maintain the plasma level of the at least one selective A1 adenosine on a concentration of 10-500 ng/ml, preferably 20-400 ng/ml, more preferably 30-300 ng/ml.

10. A use according to any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9, wherein the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist is selected from pyrrolo[2,3d]pyrimidine derivatives of formula I,
as defined in claim 1,
and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof.

11. A use according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, wherein the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist is selected from 4-[(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-trans-cyclohexanol methanesulfonate or (4S)-4-hydroxy-1-(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-L-prolinamide methanesulfonate, and/or a prodrug, and/or a solvate thereof.

12. A use according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11, wherein said at least one radiopaque media is an iopanoic acid, gadolinium-based radiopaque media selected from the group consisting of bunaoid, biligram, bilimiro, bilopaque, choliniol, ethiodol, diatrain, dionosil, failignost, gadoxobutrol, gadodiamide, gadopen-
tetate dimeglumine, gastrografin, hexabrix, hippodin, manigafodipir, amidotrizoate, ethiodized oil, imagopaque, iodamide, iodipamide, iodixanol, iodophene, iophendylate, iomeron, iomeprol, iopamidol, iopanoic acid, iopiperidol, iophendylate, iopromide, iopydol, isosmenol, iothalamic acid, iotrolan, ioversol, ioxilan, ioxaglic acid, isopaque, ipodate, meglumine iothalamate, meglumine acetrizoate, meglumine diatrizoate, metrizamide, myelotraft, omnipaque, osbil, optiray, optojod, opacoron, perfluorbenziodiol, phentetiothaiein sodium, priodax, propylidone, skiodan, sodium iodomethamate, sodium diatrizoate, telepaque, teridax, tetabrom, thoro-
trast, triognost, 1,3,5-Tri-n-hexyl-2,4,6-trriiodobenzene, tyropanoate, visipaque or xenetix, and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a sol-
vate thereof.

AMENDED SHEET (ARTICLE 19)
13. A use according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12, wherein the medicament is a fixed combination.

14. A pharmaceutical combination comprising

a) a therapeutically effective amount of at least one selective adenosine A1 antagonist of formula I,

![Chemical Structure](image)

wherein

R1 and R2 are each independently selected from a hydrogen atom, an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety or together form an optionally substituted heterocyclic ring;
R3 is selected from a hydrogen atom or an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety;
R4 and R5 are each independently selected from a halogen atom, a hydrogen atom or an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety, or R4 and R5 together form an optionally substituted heterocyclic or optionally substituted carbocyclic ring;
and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof and

b) at least one radiocontrast media,

wherein the pharmaceutical combination being suitable for simultaneous, separate or step-wise administration to humans or mammals.

15. A pharmaceutical combination according to claim 14 comprising

a therapeutically effective amount of at least one selective adenosine A1 antagonist of formula I,

wherein
R1 and R2 are each independently selected from a hydrogen atom, an optionally substituted alkyl or together form an optionally substituted heterocyclic ring;
R3 is a hydrogen atom or an optionally substituted aryl;

AMENDED SHEET (ARTICLE 19)
R4 and R5 are each independently selected from a halogen atom or a hydrogen atom;
preferably wherein
R1 is a hydrogen and R2 is an optionally substituted cyclohexyl ring, or R1 and R2
together form an optionally substituted pyrrolidine ring;
R3 is a phenyl ring;
R4 and R5 are each a hydrogen atom;
and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof and
10  a) at least one radiocontrast media,
wherein the pharmaceutical combination being suitable for simultaneous, separate
or step-wise administration to humans or mammals.

16. A pharmaceutical combination according to claim 15 comprising
a) a therapeutically effective amount of at least one selective adenosine A1 an-
tagonist selected from 4-[(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-trans-
cyclohexanol methanesulfonate or (4S)-4-hydroxy-1-(2-phenyl-7H-pyrrolo[2,3-
d]pyrimidin-4-yl)-L-prolinamide methanesulfonate, and/or a prodrug, and/or a sol-
20  vate thereof and
b) at least one radiocontrast media,
wherein the pharmaceutical combination being suitable for simultaneous, separate
or step-wise administration to humans or mammals.

17. A pharmaceutical combination according to any of claims 14, 15 or 16 comprising
a therapeutically effective amount of said at least one selective adenosine A1 re-
ceptor antagonist to be administered intravenously in a loading dosage and com-
25  promising a maintenance dosage, and the amount of the at least one selective
adenosine A1 receptor antagonist loading dosage to be administered at a time pe-
period of 5-25 minutes, preferably 10-20 minutes, more preferably of 13-17 minutes,
more preferably 15 minutes prior to the administration of said at least one radio-
30  contrast media, and comprising the maintenance dosage of the at least one selec-
tive adenosine A1 receptor antagonist to be administered over a period of up to 48
hours subsequent to administration of the loading dosage of said at least one se-
selective A1 receptor antagonist.
18. A pharmaceutical combination according to any of claims 14, 15, 16 or 17 comprising the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist in an orally, preferably in an extended release formulation, to be administered prior to the administration of the at least one radiocontrast agent.

19. A pharmaceutical combination according to any of claims 14, 15, 16, 17 or 18, comprising the at least one radiocontrast media to be not earlier administered until the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist is sufficient to provide a plasma level of a concentration of 10-500 ng/ml, preferably 20-400 ng/ml, more preferably 30-300 ng/ml.

20. A pharmaceutical combination according to any of claims 14, 15, 16, 17, 18 or 19, wherein the time period of application of the at least one selective A1 adenosine antagonist is sufficient to maintain the plasma level of the at least one selective A1 adenosine antagonist on a concentration of 10-500 ng/ml, preferably 20-400 ng/ml, more preferably 30-300 ng/ml.

21. A pharmaceutical combination according to any of claims 14, 15, 16, 17, 18, 19 or 20, wherein said at least one radiocontrast media is an iodinated or gadolinium-based radiocontrast media selected from the group consisting of bunaidod, biligram, bilimiro, bilopaque, cholimil, ethiodol, diatras, dionosil, fatignost, gadobutrol, gadodiamide, gadopentetate dimeglumine, gastrografin, hexabrix, hippocin, mangafodipir, amidotrizoate, ethiodized oil, imagopaque, iodamide, iodipamide, iodixanol, iodophene, iophendylate, isomeron, iomeprol, iopamidol, iopanoic acid, iopiperidol, iophendylate, iopromide, iopydol, iosimenol, iothalamic acid, iotrolan, ioversol,ioxilan, ioxaglic acid, isopaque, ipodate, meglumine iothalamate, meglumine acetrizoate, meglumine diatrizoate, metrizamide, myelotrace, omnipaque, osbil, optiray, optijod, opacoron, perfluerten, phenobutiodil, phenetiothalein sodium, priodax, propylidone, skiodan, sodium iodomethamate, sodium diatrizoate, telepaque, teridax, tetabrom, thorotrast, triognost, 1,3,5-Tri-n-hexyl-2,4,6-triiodobenzene, tyropanoate, visipaque or xenetix, and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof.

22. A kit comprising

AMENDED SHEET (ARTICLE 19)
a) a therapeutically effective amount of at least one selective adenosine A1 antagonist of formula I

wherein

R1 and R2 are each independently selected from a hydrogen atom, an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety or together form an optionally substituted heterocyclic ring;

R3 is selected from a hydrogen atom or an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety;

R4 and R5 are each independently selected from a halogen atom, a hydrogen atom or an optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkylaryl moiety, or R4 and R5 together form an optionally substituted heterocyclic or optionally substituted carbocyclic ring;

and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof and

b) at least one radiopaque media.

wherein the pharmaceutical combination being suitable for simultaneous, separate or step-wise administration to humans or mammals.

23. A kit according to claim 22 comprising

a) a therapeutically effective amount of at least one selective adenosine A1 antagonist of formula I

wherein

R1 and R2 are each independently selected from a hydrogen atom, an optionally substituted alkyl or together form an optionally substituted heterocyclic ring;

R3 is a hydrogen atom or an optionally substituted aryl;

R4 and R5 are each independently selected from a halogen atom or a hydrogen atom;

preferably wherein

R1 is a hydrogen and R2 is an optionally substituted cyclohexyl ring, or R1 and R2 together form an optionally substituted pyrrolidine ring;

AMENDED SHEET (ARTICLE 19)
R3 is a phenyl ring;
R4 and R5 are each a hydrogen atom;
and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof and
b) at least one radiocontrast media.
wherein the pharmaceutical combination being suitable for simultaneous, separate or step-wise administration to humans or mammals.

24. A kit according to claim 23 comprising

a) a therapeutically effective amount of at least one selective adenosine A1 antagonist selected from 4-[(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]trans-cyclohexanol methanesulfonate or (4S)-4-hydroxy-1-(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-L-prolinamide methanesulfonate, and/or a prodrug, and/or a solvate thereof and

b) at least one radiocontrast media.
wherein the pharmaceutical combination being suitable for simultaneous, separate or step-wise administration to humans or mammals.

25. A kit according to any of claims 22, 23 or 24, comprising

a) a loading dosage container of the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist to be administered intravenously

b) a maintenance dosage container of the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist to be administered intravenously

c) at least one radiocontrast media
comprising the at least one selective adenosine A1 receptor antagonist to be administered intravenously in a loading dosage and comprising a maintenance dosage, and the amount of the at least one selective adenosine A1 receptor antagonist loading dosage to be administered at a time period of 5-25 minutes, preferably 10-20 minutes, more preferably of 13-17 minutes, more preferably 15 minutes prior to the administration of said at least one radiocontrast media, and comprising the maintenance dosage of the at least one selective adenosine A1 receptor antagonist to be administered over a period of up to 48 hours subsequent to administration of the loading dosage of said at least one selective A1 receptor antagonist.
26. A kit according to any of claims 22, 23 or 24 comprising
   a) a container with the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist to be administered orally
   b) at least one radiocontrast media
   comprising the at least one selective adenosine A1 receptor antagonist in an orally, preferably in an extended release formulation, to be administered prior to the administration of the at least one radiocontrast agent.

27. A kit according to any of claims 22, 23, 24, 25 or 26 comprising the therapeutically effective amount of said at least one radiocontrast media to be not earlier administered until the therapeutically effective amount of said at least one selective adenosine A1 receptor antagonist is sufficient to provide a plasma level of a concentration of 10-500 ng/ml, preferably 20-400 ng/ml, more preferably 30-300 ng/ml.

28. A kit according to any of claims 22, 23, 24, 25, 26 or 27, wherein the time period of application of the therapeutically effective amount of said at least one selective A1 adenosine antagonist is sufficient to maintain the plasma level of the at least one selective A1 adenosine on a concentration of 10-500 ng/ml, preferably 20-400 ng/ml, more preferably 30-300 ng/ml.

29. A kit according to any of claims 22, 23, 24, 25, 26, 27 or 28, wherein said at least one radiocontrast media is an iodinated or gadolinium-based radiocontrast media selected from the group consisting of buniadil, biligram, bilimiro, bilopaque, cholimil, ethiodol, diatrasol, dionosil, falignost, gadobutrol, gadodiamide, gadopentetate dimeglumine, gastrografin, hexabrix, hippodin, mangafodipir, amidotrizoate, ethiodized oil, imagopaque, iodamide, iodipamide, ioxixanol, iodophene, iophendylate, iomeron, iomeprol, iopamidol, iopanoic acid, iopiperidol, iophendylate, iopromide, iopydol, iosimenol, iothalamic acid, iotrolan, ioversol, ioxilan,ioxaglic acid, isopaque, ipodate, meglumine iothalamate, meglumine acetrizoate, meglumine diatrizoate, metrizamide, myelotраст, omnipaque, osbil, optiray, optojod, opacoron, perfluotren, phenobutiodil, phentetiothalein sodium, priodax, propyliodone, skiodan, sodium iodomethamate, sodium diatrizoate, telepaque, teridax, tetrabrom, thornotrazt, triognost, 1,3,5-Tri-n-hexyl-2,4,6-triliodobenzene, tyropanoate, visipaque or

AMENDED SHEET (ARTICLE 19)
xenetix, and/or a pharmaceutically acceptable salt, and/or a prodrug, and/or a solvate thereof.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/519 A61K51/00 A61P13/12

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)
A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search:

11 October 2007

Date of mailing of the international search report:

18/10/2007

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx: 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer:
Economou, Dimitrios

Form PCT/ISA/210 (second sheet) (April 2005)

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