Methods for limiting acute kidney injury

Cross Reference

This application claims priority to U.S. Provisional Patent Application Serial Nos. 62/078299 filed November 11, 2014; 62/130435 filed March 9, 2015; and 62/169996 filed June 2, 2015, each incorporated by reference herein in their entirety.

Background

Acute kidney injury (AKI) — also called acute renal/kidney failure— develops rapidly over a period of a few hours or days. AKI can lead to chronic kidney disease (CKD), or even kidney failure needing dialysis (end-stage kidney disease). It may also lead to heart disease or death.

Summary of the Invention

In one aspect, the invention provides methods of limiting development of acute kidney injury (AKI), comprising administering to a subject to be subjected to a precipitating event an amount effective of pyridoxamine, or a pharmaceutically acceptable salt thereof, to limit development of the AKI, wherein the administering comprises administering pyridoxamine, or a pharmaceutically acceptable salt thereof, to the subject prior to, at the time of, or within 24 hours of the precipitating event. In another aspect, the invention provides methods of limiting development of acute kidney injury (AKI), comprising administering to a subject at risk of AKI an amount effective of pyridoxamine, or a pharmaceutically acceptable salt thereof, to limit development of the AKI. In a further aspect, the invention provides methods of treating development of acute kidney injury (AKI), comprising administering to a subject with AKI an amount effective of pyridoxamine, or a pharmaceutically acceptable salt thereof, to treat AKI. In a still further aspect, the invention provides methods for monitoring efficacy of pyridoxamine therapy, comprising

(a) determining one or more of the following in a biological sample obtained from a subject receiving pyridoxamine therapy (a) expression level of Col3α1, (b) expression level of αSMA, (c) expression level of Kim1, (d) expression level of NGAL, (e) expression level of Col1α1, and/or (e) isofuran-to-isoprostane ratio (IsoF/IsoP); and

(b) comparing the levels of markers determined in step (a) to a control;

wherein those subjects with a decreased level of one or more of the markers compared to control are responding to pyridoxamine therapy.

In another aspect, there is provided use of an amount effective of pyridoxamine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for limiting development of acute kidney injury (AKI), wherein the pyridoxamine, or a pharmaceutically acceptable salt thereof is to be administered to a subject prior to, at the time of, or within 24 hours of a precipitating event.

In another aspect, there is provided use of an amount effective of pyridoxamine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for limiting development of acute kidney injury (AKI).

In another aspect, there is provided use of an amount effective of pyridoxamine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating development of acute kidney injury (AKI).

Description of the Figures

Figure 1. Dose dependent effects of pre-treatment with pyridoxamine (PYR) at 500 and 1000 mg/kg/day on renal fibrosis 28 days after I/R-AKI. (A) Experimental model. Mice underwent unilateral renal pedicle clamping (U-IR) followed by contralateral nephrectomy 8 days after the initial surgery. All mice were pre-treated for 3 days with either vehicle control, or PYR 500 and 1000 mg/kg/day in drinking water supplemented with 200 mg PYR twice a day (or vehicle) by oral gavage for 3 days after each surgical procedure. Treatment was continued for 28 days at which point mice were sacrificed and kidney harvested for analysis. (B-D) Expression of renal fibrosis markers Col1α1, α-SMA and Col3α1 mRNA relative to Gapdh mRNA control. (E) Quantification of Sirius red stained (% total area). (F) Representative images for Sirius red stained tissues (outer medulla; scale bars, 50μm). Results expressed as mean +/- SEM, n=9-10 mice per group. Results only indicated if ANOVA $p<0.05$: *$p<0.05$, **$p<0.01$, ***$p<0.001$, #$p<0.0001$. Comparison with uninjured controls (no brackets), or vehicle treated mice (brackets).

Figure 2. Dose dependent effects of pre-treatment with PYR at 500 and 1000 mg/kg/day on markers of renal injury 28 days after I/R-AKI. Effect of PYR on Kim1 (A) and NGAL (B) mRNA on day 28 after injury. Results expressed as mean +/- SEM, n=9-10 mice per group. Results only indicated if ANOVA $p<0.05$: *$p<0.05$, **$p<0.01$, ***$p<0.001$, #$p<0.0001$. Comparison with uninjured controls (no brackets), or vehicle treated mice (brackets).

Figure 3. Beneficial effects of treatment with PYR at 1000 mg/kg/day started 24 hours after injury on renal fibrosis 28 days after I/R-AKI. (A) Experimental model. Mice underwent U-IR followed by contralateral nephrectomy 8 days after the initial surgery. Mice were treated with PYR 1000mg/kg/day starting 24 hours after the initial injury supplemented with 200mg PYR twice a day (or vehicle) by oral gavage for 3 days after each surgical procedure. Treatment was continued for 28 days at which point mice were sacrificed and kidney harvested for analysis. (B-D) Expression of renal fibrosis markersCol1α1, α-SMA and Col3α1 mRNA relative to Gapdh mRNA control. (E) Quantification of Sirius red stained (% total area). (F) Representative images for Sirius red stained tissues (outer medulla; scale bars,

We claim

1. Use of an amount effective of pyridoxamine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for limiting development of acute kidney injury (AKI), wherein the pyridoxamine, or a pharmaceutically acceptable salt thereof is to be administered to a subject prior to, at the time of, or within 24 hours of a precipitating event.

2. The use of claim 1 wherein the precipitating event is selected from the group consisting of cardiovascular surgery, injection of a contrast dye, administration of chemotherapeutic agents, development of an infection-induced inflammation (sepsis), and admission to a hospital intensive care unit.

3. Use of an amount effective of pyridoxamine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for limiting development of acute kidney injury (AKI).

4. The use of claim 3, wherein the subject has a risk factor for AKI selected from the group consisting of low blood volume, liver cirrhosis, infection-induced inflammation (sepsis), renal artery stenosis, renal vein thrombosis, glomerulonephritis, acute tubular necrosis (ATN), acute interstitial nephritis (AIN), benign prostatic hyperplasia, exposure to an obstructed urinary catheter, bladder stone; and bladder, ureteral or renal malignancy.

5. The use of any one of claims 1-4, wherein limiting the development of AKI comprises one or more of the following:

- Limiting the increase in serum creatinine levels characteristic of AKI;
- Limiting the decrease in glomerular filtration rate characteristic of AKI;
- Reducing the decrease in urine volume characteristic of AKI;
- Limiting the renal fibrosis characteristic of AKI;
- Limiting development of one or more other symptoms of AKI, including but not limited to metabolic acidosis, high potassium levels (and potentially resulting irregular heartbeat), uremia, changes in body fluid balance, and effects to other organ systems;
- Limiting progression to chronic renal disease;
- Limiting need for renal dialysis; and
- Limiting need for kidney transplant.

6. Use of an amount effective of pyridoxamine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating development of acute kidney injury (AKI).

7. The use of claim 6, wherein treating AKI comprises one or more of:

- Reducing or limiting the increase in serum creatinine levels characteristic of AKI;
- Increasing or limiting the decrease in glomerular filtration rate characteristic of AKI;
- Reducing the decrease in urine volume characteristic of AKI;
- Limiting the renal fibrosis characteristic of AKI;
- Limiting development of one or more other symptoms of AKI, including but not limited to metabolic acidosis, high potassium levels (and potentially resulting irregular heartbeat), uremia, changes in body fluid balance, and effects to other organ systems;
- Limiting progression to chronic renal disease;
- Limiting need for renal dialysis; and
- Limiting need for kidney transplant.

8. The use of any one of claims 1-7, wherein the pyridoxamine or pharmaceutically acceptable salt thereof is administered to the subject at least once per day at a dosage unit of between 1 mg/kg and 1000 mg/kg.

9. A method for monitoring efficacy of pyridoxamine therapy, comprising

(a) determining one or more of the following in a biological sample obtained from a subject receiving pyridoxamine therapy (a) expression level of Col3α1, (b) expression level of αSMA, (c) expression level of Kim1, (d) expression level of NGAL, (e) expression level of Col1α1, and/or (e) isofuran-to-isoprostane ratio (IsoF/IsoP); and

(b) comparing the levels of markers determined in step (a) to a control;

wherein those subjects with a decreased level of one or more of the markers compared to control are responding to pyridoxamine therapy.

10. The method of claim 9, wherein the subject has AKI.

11. The method of claim 9 or 10, wherein a subsequent dosage of pyridoxamine, or a pharmaceutical salt thereof, to the subject is increased if the level of the one or more markers is not increased in the biological sample.