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 the 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 up to 3 days, or within 24 hours of a precipitating event, wherein the precipitating event is cardiovascular surgery. In another aspect, the invention refers to 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 Col1α1, and/or (d) 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 one example, the present disclosure refers to 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 example, the disclosure 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 example, the disclosure 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 example, the disclosure 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.

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).

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 up to 3 days, or within 24 hours of a precipitating event, wherein the precipitating event is cardiovascular surgery.

2. The use of claim 1, wherein the pyridoxamine, or a pharmaceutically acceptable salt thereof, is to be administered to the subject up to 3 days prior to, or at the time of the precipitating event.

3. The use of claim 1, wherein the pyridoxamine, or a pharmaceutically acceptable salt thereof, is to be administered to the subject within 24 hours of the precipitating event.

4. The use of any one of claims 1-3, 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.

5. The use of any one of claims 1-4, wherein the pyridoxamine or pharmaceutically acceptable salt thereof is to be administered to the subject at least once per day at a dosage unit of between 1 mg/kg and 1000 mg/kg.

6. 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 Col1α1, and/or (d) 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.

7. The method of claim 6, wherein the subject has AKI.

8. The method of claim 6 or 7, 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.

9. The method of any one of claims 6-8, wherein the biological sample comprises a kidney biopsy.

10. The use of any one of claims 1-5, or the method of any one of claims 6-9,wherein the subject is a mammal.

11. The use of any one of claims 1-5, or the method of any one of claims 6-9,wherein the subject is a human.