

High Dose of NSAIDs May Increase Kidney Disease Risk

Exposure to high doses of nonsteroidal anti-inflammatory drugs (NSAIDs) shows a modest but significant association with kidney disease in a military population, reports a study in the open-access journal *JAMA Network Open*.

The retrospective analysis included data on more than 764,000 US Army soldiers on active duty from 2011 through 2014. Eighty-six percent of participants were men; median age was 27 years. Dispens-

ing and dose of prescription NSAIDs were evaluated for association with incident diagnoses of acute kidney injury (AKI) and chronic kidney disease (CKD).

The participants received a total of 1.6 million distinct NSAID prescriptions during the observation period: mean 2.1 prescriptions per person. Nearly two-thirds of personnel had no NSAID prescriptions in the previous 6 months. About 18% were dispensed 1 to 7 mean total daily defined

doses (DDD) per month, while 16% received more than 7 DDDs. There were a total of 2356 AKI outcomes, affecting 0.3% of participants; and 1634 CKD outcomes, affecting 0.2% of participants.

Participants with 7 or more DDDs per month had significant increases in both kidney disease outcomes: adjusted hazard ratio 1.2 for both AKI and CKD. At this level of exposure, there were 17.6 additional cases of AKI and 30.0 additional cases

of CKD per 100,000 exposed individuals. Obese individuals were at significantly increased risk of both outcomes: adjusted hazard ratio 1.5 for AKI and 1.6 for CKD. The hazards were more than doubled for individuals with a history of hypertension and rhabdomyolysis. For diabetes, the hazard ratio was 1.8 for both outcomes.

Most studies of NSAID associations with kidney disease have focused on older adults or patients with chronic diseases. There has been little concern about the renal effects of these widely used medications in young, healthy adults. Some studies have suggested a possible increase in kidney disease risk among NSAID users engaging in endurance exercise.

This large study of Army personnel finds “modest but statistically significant” associations between high doses of NSAIDs and the risk of acute and chronic kidney disease outcomes. “Dosage reduction represents an approach that may decrease associated kidney disease outcome rates,” the researchers write. They also note the contribution of modifiable factors such as body mass index and hypertension [Nelson DA, et al. Association of nonsteroidal anti-inflammatory drug prescriptions with kidney disease among active young and middle-aged adults. *JAMA New Open* 2019; 2(2):e187896. doi:10.1001/jamanetworkopen.2018.7896]. ■

Auryxia®

(ferric citrate) tablets

AURYXIA® (ferric citrate) tablets for oral use containing 210 mg of ferric iron equivalent to 1 g AURYXIA for oral use.

INDICATION AND USAGE

AURYXIA is indicated for the control of serum phosphorus levels in adult patients with chronic kidney disease on dialysis.

CONTRAINDICATIONS

AURYXIA is contraindicated in patients with iron overload syndromes (e.g., hemochromatosis).

WARNINGS AND PRECAUTIONS

Iron Overload: Iron absorption from AURYXIA may lead to excessive elevations in iron stores. Increases in serum ferritin and transferrin saturation (TSAT) levels were observed in clinical trials. In a 56-week safety and efficacy trial evaluating the control of serum phosphate levels in patients with chronic kidney disease on dialysis in which concomitant use of intravenous iron was permitted, 55 (19%) of patients treated with AURYXIA had a ferritin level >1500 ng/mL as compared with 13 (9%) of patients treated with active control.

Assess iron parameters (e.g., serum ferritin and TSAT) prior to initiating AURYXIA and monitor iron parameters while on therapy. Patients receiving intravenous iron may require a reduction in dose or discontinuation of intravenous iron therapy.

Risk of Overdosage in Children Due to Accidental Ingestion:

Accidental ingestion and resulting overdose of iron-containing products is a leading cause of fatal poisoning in children under 6 years of age. Advise patients of the risks to children and to keep AURYXIA out of the reach of children.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to adverse reaction rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Hyperphosphatemia in Chronic Kidney Disease on Dialysis

A total of 289 patients were treated with AURYXIA and 149 patients were treated with active control (sevelamer carbonate and/or calcium acetate) during the 52-week, randomized, open-label, active control phase of a trial in patients on dialysis. A total of 322 patients were treated with AURYXIA for up to 28 days in three short-term trials. Across these trials, 557 unique patients were treated with AURYXIA; dosage regimens in these trials ranged from 210 mg to 2,520 mg of ferric iron per day, equivalent to 1 to 12 tablets of AURYXIA.

Adverse reactions reported in more than 5% of patients treated with AURYXIA in these trials included diarrhea (21%), discolored feces (19%), nausea (11%), constipation (8%), vomiting (7%), and cough (6%).

During the 52-week, active-control period, 61 patients (21%) on AURYXIA discontinued study drug because of an adverse reaction, as compared to 21 patients (14%) in the active control arm. Patients who were previously intolerant to any of the active control treatments (calcium acetate and sevelamer carbonate) were not eligible to enroll in the study. Gastrointestinal adverse reactions were the most common reason for discontinuing AURYXIA (14%).

DRUG INTERACTIONS

Orally administered doxycycline has to be taken at least 1 hour before AURYXIA. Orally administered ciprofloxacin should be taken at least 2 hours before or after AURYXIA. Oral drugs that can be administered concomitantly with AURYXIA are: amlodipine, aspirin, atorvastatin, calcitriol, clopidogrel, digoxin, diltiazem, doxercalciferol, enalapril, fluvastatin, glimepiride, levofloxacin, losartan, metoprolol, pravastatin, propranolol, sitagliptin, and warfarin.

Oral medications not listed above

There are no empirical data on avoiding drug interactions between AURYXIA and most concomitant oral drugs. For oral medications where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, consider separation of the timing of the administration of the two drugs. The duration of separation depends upon the absorption characteristics of the medication concomitantly administered, such as the time to reach peak systemic levels and whether the drug is an immediate release or an extended release product. Consider monitoring clinical responses or blood levels of concomitant medications that have a narrow therapeutic range.

USE IN SPECIFIC POPULATIONS

Pregnancy:

Risk Summary

There are no available data on AURYXIA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Animal reproduction studies have not been conducted using AURYXIA. Skeletal and encephalic malformation was observed in neonatal mice when ferric gluconate was administered intraperitoneally to gravid dams on gestation days 7-9. However, oral administration of other ferric or ferrous compounds to gravid CD1-mice and Wistar-rats caused no fetal malformation.

An overdose of iron in pregnant women may carry a risk for spontaneous abortion, gestational diabetes and fetal malformation. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20% respectively.

Clinical Considerations

The effect of AURYXIA on the absorption of vitamins and other nutrients has not been studied in pregnant women. Requirements for vitamins and other nutrients are increased in pregnancy.

Lactation:

Risk Summary

There are no human data regarding the effect of AURYXIA in human milk, the effects on the breastfed child, or the effects on milk production. Data from rat studies have shown the transfer of iron into milk by divalent metal transporter-1 (DMT-1) and ferroportin-1 (FPN-1). Hence, there is a possibility of infant exposure when AURYXIA is administered to a nursing woman. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for AURYXIA and any potential adverse effects on the breastfed child from AURYXIA or from the underlying maternal condition.

Pediatric Use: The safety and efficacy of AURYXIA have not been established in pediatric patients.

Geriatric Use: Clinical studies of AURYXIA included 292 subjects aged 65 years and older (104 subjects aged 75 years and older). Overall, the clinical study experience has not identified any obvious differences in responses between the elderly and younger patients in the tolerability or efficacy of AURYXIA.

OVERDOSAGE

No data are available regarding overdose of AURYXIA in patients. In patients with chronic kidney disease, the maximum dose studied was 2,520 mg ferric iron (12 tablets of AURYXIA) per day. Iron absorption from AURYXIA may lead to excessive elevations in iron stores, especially when concomitant intravenous iron is used.

In clinical trials, one case of elevated iron in the liver as confirmed by biopsy was reported in a patient on dialysis administered intravenous iron and AURYXIA.

PATIENT COUNSELING INFORMATION

Dosing Recommendations: Instruct patients to take AURYXIA as directed with meals and adhere to their prescribed diets. Instruct patients on concomitant medications that should be dosed apart from AURYXIA. Advise patients not to chew or crush AURYXIA because tablets may cause discoloration of mouth and teeth.

Adverse Reactions: Advise patients that AURYXIA may cause discolored (dark) stools, but this staining of the stool is considered normal with oral medications containing iron.

AURYXIA may cause diarrhea, nausea, constipation, vomiting, hyperkalemia, abdominal pain, and cough. Advise patients to report severe or persistent gastrointestinal symptoms to their physician.

Accidental Ingestion: Advise patients to keep this product out of the reach of children and to seek immediate medical attention in case of accidental ingestion by a child.

Issued 11/2017 Rev 4.0



©2019 Akebia Therapeutics.

Printed in USA

PP-AUR-US-0760

01/19

Markers of Tubule Cell Dysfunction Predict AKI

Among patients with chronic kidney disease (CKD), baseline biomarkers of tubule cell function are independent predictors of the later development of acute kidney injury (AKI), reports a study in *Kidney International*.

The researchers analyzed data on 2351 participants from the randomized Systolic Blood Pressure Intervention Trial (SPRINT). All had CKD (mean estimated glomerular filtration rate [eGFR] 49 mL/min/1.73 m²) and hypertension at baseline, but not diabetes. Participants were assigned intensive or standard systolic blood pressure targets: less than 120 versus less than 140 mm Hg. Study outcomes showed lower rates of cardiovascular disease and death with intensive blood pressure-lowering therapy, but a higher risk of AKI.

The current study analyzed baseline data on urinary markers of renal tubule dysfunction (alpha-1-microglobulin [α 1m], beta-2 microglobulin [β 2m], and uromodulin [UMOD]) and markers of renal tubule injury (kidney injury molecule-1 [KIM-1], neutrophil gelatinase-associated lipocalin [NGAL], interleukin-18 [IL-18], monocyte chemoattractant protein-1 [MCP-1]) and chitinase-3-like protein [YKL-40]). The two types of markers were analyzed for association with the risk of AKI, with adjustment for other factors.

Over a mean follow-up of 3.8 years, AKI developed in 184 participants—a rate of 7.8%. Acute kidney injury was more frequent in men and in black patients, as well as those assigned to the intensive blood pressure–lowering therapy.

Two markers of kidney tubular dysfunction—UMOD and $\alpha 1m$ —were associated with AKI, independent of eGFR and albuminuria. Hazard ratios were 0.68 per twofold increase in UMOD and 1.20 per twofold increase in $\alpha 1m$. At the highest versus lowest quartiles, baseline UMOD and $\alpha 1m$ were more strongly associated with AKI risk (HR 2.04 and 1.57, respectively) compared to the 3-month change in serum creatinine (HR 1.27). In contrast, increases of tubule cell injury markers occurred mainly after the AKI event.

Identifying CKD patients at particularly high risk of AKI may help to inform monitoring and prevention strategies. This study identifies markers of tubule cell dysfunction—lower UMOD and higher $\alpha 1m$ —as predictors of future AKI risk. The researchers conclude: “[T]ubular cell function markers may reflect a vulnerable kidney with diminished capacity to counter acute insults and thus identify CKD individuals at heightened risk of future AKI” [Bullen AL, et al. The SPRINT trial suggests that markers of tubule cell function in the urine associate with risk of subsequent acute kidney injury while injury markers elevate after the injury. *Kidney Int* 2019; DOI: <https://doi.org/10.1016>]. ■

Dual Therapies for Black African Patients: Randomized Trial

Combination therapies including amlodipine improve blood pressure (BP) control in sub-Saharan African patients with hypertension, concludes a trial in *The New England Journal of Medicine*.

The randomized controlled “Comparison of Three Combination Therapies in Lowering Blood Pressure in Black Africans” (CREOLE) trial included 728 black patients with uncontrolled hypertension in six sub-Saharan African countries. Enrolled patients had BP of 140/90 mm Hg or higher on no antihypertensive therapy or a single-drug regimen. The patients’ average age was 51 years; 63% were women.

Patients were assigned to one of three antihypertensive drug combinations: the calcium-channel blocker amlodipine (5 mg) plus the thiazide diuretic (HCTZ) (12.5 mg); amlodipine plus the angiotensin-converting enzyme inhibitor perindopril (4 mg); or perindopril plus HCTZ. After 2 months, the dose of each drug was doubled for another 4 months (amlodipine 10 mg, hydrochlorothiazide 25 mg, perindopril 8 mg). Change in 24-hour ambulatory systolic BP from baseline to 6 months was compared between groups.

On analysis of primary outcome data in 621 patients, reductions in BP were greater with the two amlodipine-containing regimens. Compared to perindopril plus HCTZ, between-group differences in systolic BP were 3.14 mm Hg with amlodipine plus HCTZ and 3.00 mm Hg with amlodipine plus perindopril. There was no significant difference between the two amlodipine regimens.

Other outcomes showed a similar pattern, including ambulatory diastolic BP, office BP, and BP response rate. Six-month BP control rates were 76%

with amlodipine-HCTZ and 74% with amlodipine-perindopril versus 60% with perindopril-HCTZ. Patients receiving amlodipine-HCTZ had significant reductions in plasma potassium and higher rates of hypokalemia.

Black African patients have a high prevalence of hypertension and typically need at least two antihypertensive drugs to achieve BP control. There is uncertainty regarding the most effective two-drug regimen for black patients with hypertension, reflected by differences in current recommendations.

The CREOLE results suggest a better response with amlodipine, combined with either HCTZ or perindopril, compared to HCTZ plus perindopril in black African patients with uncontrolled hypertension. The researchers note some limitations of their study, including whether the findings can be generalized to black patients with diabetes or those outside of sub-Saharan Africa [Ojji DB, et al. Comparison of dual therapies for lowering blood pressure in black Africans. *N Engl J Med* 2019; DOI: 10.1056/NEJMoa1901113]. ■



ASN Board Review Course & Update

July 20–25, 2019 | Chicago, IL
Fairmont Chicago Millennium Park

Early
Registration
Deadline:
June 20

Maximize your readiness for the nephrology board examinations.

Register for ASN’s Board Review Course & Update (BRCU). This intensive, six-day course provides a detailed review of key nephrology concepts. Taught by leading experts in the field, BRCU is the best way to prepare for the ABIM nephrology board certification and recertification examinations.

Highlights

- Exam-focused curricula
- Interactive case-based studies
- Printed course books
- “How to Study for the Boards; How to Approach a Board Question” presentation
- Complimentary online access to all lectures after the course
- Online practice exam with 300+ questions
- Up to 65.25 CME Credits and MOC Points
- Nephrology Board “Pearls of Wisdom” to help focus studying

Learn more at
www.asn-online.org/BRCU