

Automated Office BP Beats Routine Readings: Meta-Analysis

Automated office blood pressure (AOBP) readings are more accurate than office measurements and should be the “preferred method” for recording BP in clinical practice, concludes a meta-analysis in *JAMA Internal Medicine*.

A systematic review of the literature identified 31 articles related to AOBP including a total of 9279 patients. All of the studies included at least 30 patients with properly recorded AOBP measurements: patient unattended and sitting in a quiet place. The studies provided data enabling

comparison of AOBP with awake ambulatory BP, research-quality office BP, or routine office BP measurements.

Mean systolic AOBP was 130 mm Hg or higher in about half of the studies, totaling 4892 patients. In these studies, the routine and research office systolic BP readings were significantly higher than the AOBP readings: pooled mean differences were 14.5 and 7.0 mm Hg, respectively.

In contrast, there was little or no difference in systolic awake ambulatory BP or AOBP measurements: pooled mean differ-

ence 0.3 mm Hg. The results were consistent for studies using different devices, and in studies including specialist/referral versus unselected patient populations.

Previous studies have reported that AOBP is more accurate than routine office BP measurement, with no “white coat effect.” The new report is the first comprehensive systematic review and meta-analysis of the evidence comparing AOBP with other measurement techniques.

Recorded properly, AOBP is more accurate than routine or even research-quality

office BP measurements, and similar to awake ambulatory BP readings. The investigators conclude: “Automated office BP should now be the preferred method for recording BP in routine clinical practice to identify patients with possible hypertension, with the diagnosis to be confirmed by 24-hour ABPM or home BP” [Roerecke M, et al. Comparing automated office blood pressure readings with other methods of blood pressure measurement for identifying patients with possible hypertension: a systematic review and meta-analysis. *JAMA Intern Med* 2019; DOI:10.1001/jamainternmed.2018.6551]. ■

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 treatment of iron deficiency anemia in adult patients with chronic kidney disease not 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.

Iron Deficiency Anemia in Chronic Kidney Disease Not on Dialysis

Across two trials, 190 patients with CKD-NDD were treated with AURYXIA. This included a study of 117 patients treated with AURYXIA and 116 patients treated with placebo in a 16-week, randomized, double-blind period and a study of 75 patients treated with AURYXIA and 73 treated with placebo in a 12-week randomized double-blind period. 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 at least 5% of patients treated with AURYXIA in these trials are listed in Table 1.

Table 1: Adverse Reactions Reported in Two Clinical Trials in at least 5% of patients receiving AURYXIA

Body System Adverse Reaction	AURYXIA % (N=190)	Placebo % (N=188)
Any Adverse Reaction	75	62
Metabolism and Nutrition Disorders		
Hyperkalemia	5	3
Gastrointestinal Disorders		
Discolored feces	22	0
Diarrhea	21	12
Constipation	18	10
Nausea	10	4
Abdominal Pain	5	2

During the 16-week, placebo-control trial, 12 patients (10%) on AURYXIA discontinued study drug because of an adverse reaction, as compared to 10 patients (9%) in the placebo control arm. Diarrhea was the most common adverse reaction leading to discontinuation of AURYXIA (2.6%).

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.

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Survival Benefit of Kidney Transplant in Lupus Nephritis

Kidney transplantation reduces mortality, mainly due to cardiovascular disease and infection, in patients with lupus nephritis, reports a study in *Annals of Internal Medicine*.

Through the United States Renal Data System, the researchers identified 20,974 individuals with kidney failure due to lupus nephritis (ESRD-LN) between 1995 and 2014. Of 9659 waitlisted patients, 5738 (59%) received a kidney transplant. Eighty-two percent of waitlisted patients were women and 60% were nonwhite.

Analyzed as a time-varying exposure, renal transplantation was associated with lower all-cause mortality among waitlisted patients: adjusted hazard ratio (HR) 0.30. There were also significant reductions in mortality due to cardiovascular disease, HR 0.26; coronary heart disease, HR 0.41; and infection or sepsis, HR 0.41 for each. The survival benefit remained significant for subgroups defined by race/ethnicity, sex, and age and throughout the study period.

Secondary analysis of a Medicare-enrolled subset included matched groups of 2963 patients with and without transplantation. Mortality rates were 21.1 and 77.1 per 1000 person-years, respectively. Adjusted HRs for death were 0.32 for deceased-donor and 0.24 for living-donor recipients.

Patients with ESRD-LN are at high risk of premature death, compared to systemic lupus erythematosus patients without kidney involvement. The survival benefit of renal transplantation in ESRD-LN patients remains unclear.

This study finds a “considerable survival benefit” of kidney transplantation in a nationwide cohort of patients with LN-ESRD. The reduction in mortality results largely from lower risks of deaths due to cardiovascular disease and infections, particularly sepsis. The researchers conclude: “Therefore, timely consideration of renal transplant should be a part of routine care for patients with LN-ESRD, and improved access to renal transplantation for this population may considerably improve outcomes” [Jorge A, et al. Renal transplantation and survival among patients with lupus nephritis: a cohort study. *Ann Intern Med* 2019; DOI: 10.7326/M18-1570]. ■