In patients undergoing major abdominal surgery, a restrictive fluid policy leads to an increased rate of acute kidney injury compared to liberal fluid therapy; while other outcomes are similar between groups, reports a study in The New England Journal of Medicine.

The “Restrictive versus Liberal Fluid Therapy in Major Abdominal Surgery” (RELIEF) trial included 3000 patients considered at increased risk of complications while undergoing major abdominal surgery. High-risk criteria included age ≥70 or older, heart disease, diabetes, renal impairment, and morbid obesity. The patients, enrolled at 47 centers in 7 countries, were randomly assigned to restrictive or liberal intravenous fluid regimens. One-year disability-free survival was compared between groups, along with a range of secondary outcomes.

Modified intention-to-treat analysis included 1490 patients assigned to the restrictive fluid strategy and 1493 to the liberal strategy. During surgery and up to 24 hours afterward, median IV fluid totals were 3.7 versus 6.1 L, respectively. There was no significant difference in disability-free survival at 1 year: 81.9% with the restrictive strategy and 82.3% with the liberal strategy.

Acute kidney injury, defined according to KDIGO criteria, was significantly more frequent in the restrictive fluid group: 8.6%, compared to 5.0% with the liberal fluid strategy. Rates of some other secondary outcomes were higher with the restrictive strategy: 2.18% versus 19.8% for septic complications or death, 16.5% versus 13.6% for surgical-site infection, and 0.9% versus 0.3% for renal replacement therapy. However, these differences were not significant after adjustment for multiple comparisons. A restrictive intravenous fluid strategy has been recommended for enhanced recovery after abdominal surgery. However, there are questions about the evidence behind this recommendation, and concern that it could lead to impaired organ perfusion.

The pragmatic RELIEF trial shows similar disability-free survival with restrictive versus liberal fluid therapy for high-risk patients undergoing major abdominal surgery. However, the restrictive strategy is associated with a significant increase in acute kidney injury.

“T[his]n study found that restricting intravenous-fluid administration with the aim of zero balance increased the risk of acute kidney injury,” the researchers write. They believe their findings show that “a regimen that includes a modestly liberal administration of fluid is safer than a restrictive regimen” [Myles PS, et al. Restrictive versus liberal fluid therapy for major abdominal surgery. N Engl J Med 2018; DOI: 10.1056/NEJMoa1801601].

Higher FGF23 Predicts Greater Increases in BP with Aging

In young to middle-aged adults, higher fibroblast growth factor-23 (FGF23) levels are independently associated with rising blood pressure levels over time, according to a report in Hypertension.

The analysis included data on a multi-ethnic cohort of 1758 adults participating in the Coronary Artery Risk Development in Young Adults (CARDIA) study. All were free of hypertension or cardiovascular disease when participating in year 20 follow-up examination. At that time, the subjects’ mean age was 45 years—about 58% were women, and 40% were black.

Levels of C-terminal FGF23 at year 20 were analyzed for association with longitudinal BP levels and hypertension at years 25 and 30. Hypertension was defined as being on antihypertensive drugs and/or BP levels of ≥130/80 mm Hg or higher.

Incident hypertension occurred in 35.2% of subjects. In multivariable models, subjects with higher FGF23 levels had greater increases in BP. For the highest compared to lowest FGF23 quartile, increases in systolic BP were +2.1 mm Hg from year 20 to 25 and +2.2 mm Hg from year 25 to 30. Being in the highest quartile of FGF23 was also associated with higher FGF23 levels at baseline.
Findings

Higher FGF23

Continued from page 9

with a greater increase in diastolic BP from year 20 to 25: +1.6 mm Hg.

Relative risk of developing hypertension during follow-up was 1.45 in the highest quartile of FGF23, compared to the lowest quartile. The lowest quartile of hypertension was higher in black than white participants: 47.7% versus 27.8%.

Although black participants and women were more likely to be in the highest quartile of FGF23, the association with incidence of hypertension did not vary by race or sex. There was also no difference based on underlying kidney disease, which was present in only a small percentage of subjects. Higher FGF23 levels have been linked to worse cardiovascular outcomes. The association of FGF23 with hypertension increases in blood pressure, or with the increased prevalence of hypertension in black Americans, has been unclear.

These CARDIA study results suggest that higher FGF23 levels are associated with rising blood pressure over time, as well as with an increased incidence of hypertension. Higher FGF23 does not appear to explain the higher rate of incident hypertension among black compared to white participants. The researchers conclude, “FGF23 could have a clinical role as a novel marker in helping to identify individuals at higher risk of developing hypertension, beyond known risk factors” [Akhabue E, et al. FGF23 (fibroblast growth factor-23) and incident hypertension in young and middle-aged adults: the CARDIA study (Coronary Artery Risk Development in Young Adults). Hypertension. 2018; https://doi.org/10.1161/HYPERTENSAHA.118.116065].

Aurxyia® (ferric citrate) tablets

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

INDICATION AND USAGE

AURXYIA is indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease not on dialysis.

CONTRAINDICATIONS

AURXYIA is contraindicated in patients with iron overload syndromes (e.g., hemosiderosis).

WARNINGS AND PRECAUTIONS

Iron Deficiency Anemia in Chronic Kidney Disease Not on Dialysis

AURXYIA should be used with caution in patients with iron deficiency anemia in chronic kidney disease not on dialysis in which concomitant use of intravenous iron was permitted, 55 (9%) of patients treated with AURXYIA had a ferritin level >1500 ng/mL, as compared with 13 (9%) of patients treated with active control.

Avoid iron parameters (e.g., serum ferritin and TSAT) prior to initiating AURXYIA 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 Overdose 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 parents about the risks to children and to keep AURXYIA 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

AURXYIA was studied in two trials, 170 unique patients with CKD-NO were treated with AURXYIA. This included a study of 117 patients treated with AURXYIA and 116 patients treated with placebo. All patients in a 15-week, randomized, double-blind period and a study of 75 patients treated with AURXYIA and 73 treated with placebo in a 12-week randomized double-blind period. Dosage regimens in these studies ranged from 2 to 2.5 mg ferrous iron per day, equivalent to 1 to 2 tablets of AURXYIA. Adverse reactions reported in at least 5% of patients treated with AURXYIA in these trials are listed in Table 1.

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>AURXYIA % (N=188)</th>
<th>Placebo % (N=188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Reaction</td>
<td>75</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>5</td>
<td>3</td>
<td></td>
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<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>18</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

During the 16-week, placebo-control trial, 12 patients (10%) on AURXYIA discontinued study drug because of an adverse reaction, as compared to 10 patients (9%) in the placebo control arm. AURXYIA was the most common adverse reaction leading to discontinuation of AURXYIA (2%).

DRUG INTERACTIONS

Orally administered doxycycline has to be taken at least 1 hour before AURXYIA. Oral medications containing iron should be taken at least 2 hours before or after AURXYIA. Oral drugs that can be administered concomitantly with AURXYA are: alendrone, aspirin, atorvastatin, calcitol, chlorpropamide, digoxin, diltiazem, doxycycline, enalapril, fluoxetine, glypride, levofloxacin, losartan, metoprolol, pravastatin, propranolol, sitagliptin, and warfarin.

Oral medications not listed above that have the bioavailability of that medication would have a clinically significant effect on the 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 is limited available data on AURXYIA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Animal reproduction studies have not been conducted using AURXYIA. Skeletal and visceral malformations were observed in newborn mice when ferrous gluconate was administered intraperitoneally to gravid dams on gestation days 7, 11, and 15. Oral administration of other ferrous or ferric 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. In humans, 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 risk of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20% respectively.

Clinical Considerations

The effect of AURXYIA 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.

Laboration: Ant-B沉重

There are no human data regarding the effect of AURXYIA 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 transporters (DMTs-1 and ferroportin-1). Hence, there is a possibility of infant exposure when AURXYIA is administered to a nursing woman. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for AURXYIA and any potential adverse effects on the breastfed child from AURXYIA or from the underlying maternal condition.

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

Geriatric Use: Clinical studies of AURXYIA included 292 subjects aged 65 years and older. In general, elderly patients should be started on a lower dosage and titrated upward until the desired effect is achieved.

Pregnancy

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

AURXYIA has been reported in this product of the reach of children. Issued 11/2017 Rev 4.0

Ambulatory BP

Beats Clinic BP for Mortality Prediction

Ambulatory blood pressure measurement are a consistently better predictor of mortality than clinic BP measurement, concludes a study in The New England Journal of Medicine.

The study included 63,910 adult primary care patients enrolled in the national Spanish Ambulatory Blood Pressure Registry from 2004 through 2014. Clinic and 24-hour blood pressure measurements were compared for associations with all-cause and cardiovascular mortality. The researchers also analyzed mortality associations for specific hypertension phenotypes: sustained hypertension (both clinic and ambulatory BP elevated), “white-coat” hypertension (elevated clinic but normal ambulatory BP), masked hypertension (normal clinic but elevated ambulatory BP), and normal BP by both measures.

Fifty-eight percent of cohort members were men; the mean age was 58 years. With a median follow-up of 4.7 years, the analysis included 3,808 deaths from any cause and 1,295 from cardiovascular causes. In a model including both sets of measurements, 24-hour systolic BP was more strongly associated with all-cause mortality compared to clinic BP: adjusted hazard ratio (HR) 1.58 versus 1.02 per 1-standard deviation increase, respectively. For nighttime and daytime ambulatory systolic BP, adjusted HRs were 1.55 and 1.54, respectively.

Associations with ambulatory BP remained stronger in subgroup analyses by age and sex, obesity, cardiovascular diseases, ethnicity, and specific hypertension phenotypes. For“white-coat” phenotype, the association with all-cause mortality was stronger for masked hypertension (HR 2.83) compared to sustained or white-coat hypertension (HR 1.80 and 1.79, respectively). Cardiovascular mortality showed similar patterns of associations with all BP phenotypes.

Based on limited data, ambulatory BP measurements are thought to better predict health outcomes compared to clinic and home measurements. These data from a Spanish national registry show that ambulatory BP measures are more strongly associated with all-cause and cardiovascular mortality compared to clinic-measured BP.

The study also lends insight into the outcomes associated with various BP phenotypes defined by ambulatory and clinic BP. The authors conclude, “White-coat hypertension was not benign, and masked hypertension was associated with a greater risk of death than sustained hypertension” [Banegas JR, et al. Relationship between clinic and ambulatory blood-pressure measurements and mortality. N Engl J Med 2018; 378:1590-1520].