Probable Drug Interaction Between Everolimus and Clarithromycin

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We present the case of a 56-year-old white man with a 6-year history of clear-cell renal cell carcinoma (T3bN0M0), left nephrectomy, obesity (136 kg), type II diabetes mellitus, hypothyroidism, anemia, and an ascending aortic aneurysm who was started on everolimus 10 mg daily 3 months prior to this incident. No everolimus levels had previously been drawn.

He was evaluated for gastrointestinal bleeding at an outside facility. Upper endoscopy revealed patchy gastritis, and he was empirically started on amoxicillin, clarithromycin, and omeprazole for suspected *Helicobacter pylori* infection (biopsy negative). Then, 12 days after initiation of this regimen, he was admitted to our facility with acute kidney injury (blood urea nitrogen = 32 mg/dL; serum creatinine = 2.8 mg/dL, baseline 1 month prior = 1.8 mg/dL), with mild proteinuria (30 mg/dL), no urine eosinophils, and an everolimus trough level of 110 ng/mL (20 hours postdose). He symptomatically endorsed fatigue and mild lower-extremity edema. He claimed excellent adherence with all medications (Table 1). He received all his medications at one local pharmacy, except for everolimus, which came from a specialty pharmacy. During his 10-day hospitalization, everolimus was withheld. He experienced persistent, asymptomatic hyperkalemia (potassium 4.8-6.1 mmol/L), which was treated with intravenous hydration, calcium gluconate, furosemide, insulin, and sodium polystyrene sulfonate. At discharge, the patient's serum creatinine and potassium returned to 2.0 mg/dL and 5.4 mmol/L, respectively, and remained stable. He was directed to discontinue the *H pylori* regimen and resume everolimus 10 mg daily with a follow-up trough 2 weeks later, which could not be obtained because of lab error. As a result, the patient's oncologist empirically decreased his everolimus dose to 5 mg daily a month after his discharge from our facility.

The manufacturer of everolimus recommends target troughs between 5 and 15 ng/mL when dosed at 4.5 mg/m^2; however, limited guidance is available when using a fixed dose of 10 mg daily for renal cell carcinoma.[1,2] Everolimus is a CYP3A4 and P-glycoprotein (PgP) substrate; therefore, concomitant use with clarithromycin, a strong CYP3A4 and PgP inhibitor, may have increased the patient's everolimus exposure.[1]

Everolimus package labeling suggests empirical dose reductions to 2.5 mg daily when administered with moderate CYP3A4/PgP inhibitors (eg, erythromycin) and discourages use with strong CYP3A4/PgP inhibitors (eg, clarithromycin).[1] A study conducted by Kovarik et al[3] found a 4.4-fold increase in everolimus AUC with concurrent erythromycin therapy. Less is known about interactions with clarithromycin. One recent case report revealed an 11.4-fold increase in levels in a previously stable everolimus fixed-dosage regimen of 1 mg every 12 hours within 11 days of initiation of clarithromycin. This occurred despite an everolimus dosage reduction to 0.25 mg every 12 hours.[4] Another report demonstrated a clarithromycin interaction in a teenaged patient receiving low-dose everolimus for heart transplant, requiring a 50% everolimus dose reduction.[5]

Table 1. Medications at the Time of the Adverse Event.

Drug	Dose	Notes
Amoxicillin	500 mg By mouth twice daily for 14 days	Started 12 days prior to admission
Clarithromycin	500 mg By mouth twice daily for 14 days	Started 12 days prior to admission
Everolimus	10 mg By mouth daily	Started 3 months prior to admission
Furosemide	40 mg By mouth every other day	
Levothyroxine	200 µg By mouth daily	
Omeprazole	40 mg By mouth daily	Started 12 days prior to admission
Metoprolol succinate	25 mg By mouth daily	

Based on the Drug Interaction Probability Scale, the causality of clarithromycin increasing everolimus exposure was evaluated as "probable" (score = 5).[6] Everolimus toxicity was a probable cause (Naranjo score = 5) of the acute kidney injury; however, multiple factors may have contributed.[7] Overdiuresis or disease progression may have played a role, but would not explain toxic everolimus concentrations. Acute interstitial nephritis caused by amoxicillin or omeprazole seem less probable without eosinophiluria.

This scenario demonstrates a probable severe drug interaction between everolimus and clarithromycin which could have been avoided with increased communication among multiple pharmacies and health care providers. This is the third case of this interaction documented in 3 years.[4,5]

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Providers should be aware of this interaction and should avoid utilizing concomitant everolimus and clarithromycin therapy.

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Declaration of Conflicting Interests

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