Use of calcium-channel blocker and antibiotic associated with small increased risk of kidney injury

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Among older adults taking a calcium-channel blocker, simultaneous use of the antibiotic clarithromycin, compared with azithromycin, was associated with a small but statistically significant greater 30-day risk of hospitalization with acute kidney injury, according to a study published by *JAMA*. The study is being published early online to coincide with its presentation at the American Society of Nephrology's Kidney Week 2013.

The commonly used antibiotics clarithromycin and erythromycin are clinically important inhibitors of the enzyme CYP3A4, while azithromycin is much less so. Calcium-channel blockers are metabolized by this enzyme. Blood concentrations of these drugs may rise to harmful levels when CYP3A4 activity is inhibited. "Currently, the U.S. Food and Drug Administration warns that 'serious adverse reactions have been reported in patients taking clarithromycin concomitantly with CYP3A4 substrates, which includes hypotension [abnormally low blood pressure] with calcium-channel blockers [that are] metabolized by CYP3A4.' Yet, calcium-channel blockers and clarithromycin continue to be frequently coprescribed in routine care," according to background information in the article. When hypotension occurs, the kidney is particularly prone to injury from poor circulation. "Despite this knowledge, the risk of acute kidney injury following coprescription of clarithromycin with a calcium-channel blocker is unknown."

Sonja Gandhi, B.Sc., of Western University, London, Canada, and colleagues conducted a study to investigate the interaction between calcium-channel blockers (amlodipine, felodipine, nifedipine, diltiazem, or verapamil) and the antibiotic clarithromycin (n = 96,226), compared with azithromycin (n = 94,083), with a focus on acute kidney injury, among older adults (average age, 76 years).

Amlodipine was the most commonly prescribed calcium-channel blocker (more than 50 percent of patients).

The researchers found that coprescribing clarithromycin with a calcium-channel blocker was associated with a higher risk of hospitalization with acute kidney injury compared with coprescribing azithromycin (0.44 percent vs. 0.22 percent); in absolute terms, coprescription with clarithromycin resulted in a 0.22 percent higher incidence of hospitalization with acute kidney injury.

When examined by type of calcium-channel blocker, the risk of hospitalization with acute kidney injury was highest among patients coprescribed clarithromycin with nifedipine (absolute risk increase, 0.63 percent). Coprescription of a calcium-channel blocker with clarithromycin was also associated with a higher risk of hospitalization with hypotension (0.12 percent vs. 0.07 percent patients taking azithromycin; absolute risk increase, 0.04 percent) and all-cause mortality (1.02 percent vs. 0.59 percent patients taking azithromycin; absolute risk increase, 0.43 percent).

"Although the absolute increases in the risks were small, these outcomes have important clinical implications. Our results suggest that potentially hundreds of hospitalizations and deaths in our region may have been associated with this largely preventable drug-drug interaction. This burden on the health care system, given the high costs of managing acute kidney injury, might have been avoided," the authors write.

"… our study highlights the need for quality improvement initiatives that will mitigate the clinical effects of such drug interactions. Potential strategies may include temporary cessation of the calcium-channel blocker for the duration of clarithromycin therapy or selection of a non-CYP3A4 inhibiting antibiotic (such as azithromycin) when clinically appropriate."

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