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Drug-Drug Interactions and Acute Kidney Injury: Caveat Prescrip

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Nephrologists are by necessity practicing pharmacologists. The kidneys play a central role in the metabolism and excretion of many drugs and are uniquely susceptible to toxic and ischemic injury from a number of drugs.¹ Nephrologists therefore must be aware of how kidney disease alters drug disposition and clearance and how drugs may cause kidney toxicity. The knowledge domain is complex: estimated glomerular filtration rate dictates drug dosing for many drugs in use that are excreted primarily by glomerular filtration. In addition, chronic kidney disease (CKD) and acute kidney injury (AKI) influence drug dosing for drugs that are not excreted by the kidney due to alterations in hepatic drug metabolism and transport.² Nephrotoxicity can arise from a variety of mechanisms, including tubular injury, intratubular obstruction/crystallization, glomerular injury, and vascular injury.³ KDIGO (Kidney Disease: Improving Global Outcomes) conducted a conference titled “Drug Prescribing in Kidney Disease: Initiative for Improved Dosing” to address the complex issues related to drug dosing in patients with decreased kidney function and shed light on this important patient safety issue.⁴

In an article recently published in the *Journal of the American Medical Association*, Gandhi et al⁵ have brought needed attention to under-recognized drug-drug interactions that increase the risk of AKI.⁵ As the number of prescribed medications increases (poly-pharmacy), so does the risk of drug-drug interactions.⁶ Nearly one-third of adults 60 years or older take 5–9 medications daily, and 12% take 10 or more. Within the field of nephrology, dialysis patients may take more than 19 pills per day,⁷ and transplant recipients typically require 5–6 medications or more per day.⁸ As a result, knowledge of clinically relevant drug-drug interactions and implementation of strategies to avoid them are important public health and safety challenges.

WHAT DOES THIS IMPORTANT STUDY SHOW?

Gandhi et al⁵ tested the real-world effect of drug-drug interactions by focusing on the known pharmacologic interaction between drugs that inhibit the cytochrome P450 3A4 enzyme (CYP3A4) and drugs that are metabolized by CYP3A4. They hypothesized that

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coadministration of a CYP3A4 inhibitor, such as clarithromycin, with a CYP3A4 substrate, such as calcium channel blockers (CCBs), would be associated with an observable increase in the risk of clinically relevant toxicity. They chose AKI as the primary end point because hypotension from elevated blood CCB levels can lead to decreased kidney perfusion and ischemic acute tubular necrosis. The highly innovative aspect of this study design was the choice of a comparison group. They did not compare the risk of side effects of CCBs/clarithromycin versus CCBs alone because this analysis would have been subject to confounding by indication (ie, those treated with both CCBs and clarithromycin may be sicker than those treated with one or the other alone; therefore, any observed difference in outcomes would be heavily biased). Instead, they compared CCB coprescription with clarithromycin against CCB coprescription with azithromycin, another macrolide antibiotic with less of an inhibitory effect on CYP3A4.

To test their hypothesis, the authors undertook a retrospective, population-based, observational cohort study of 190,309 patients who were coprescribed clarithromycin ($n = 96,226$) or azithromycin ($n = 94,083$) with a CCB (amlodipine, felodipine, nifedipine, or verapamil). The authors combined relevant information from a number of databases that permitted patient-level analyses of Ontario citizens 65 years or older. The databases contained information for demographics, vital status, drug prescriptions, hospitalization data including administrative codes, and infection type in 50% of the cohort. They assessed outcomes 30 days from the date of prescription of the macrolide antibiotic using hospital diagnostic codes for AKI. They found that coprescription of a CCB with clarithromycin, versus coprescription of a CCB with azithromycin, was associated with a higher risk of hospitalization with AKI (odds ratio [OR], 1.98; 95% confidence interval [CI], 1.68–2.34), higher risk of hypotension (OR, 1.60; 95% CI, 1.18–2.16), and greater all-cause mortality (OR, 1.74; 95% CI, 1.57–1.9). To estimate the magnitude of the effect in more clinical terms, they calculated the number needed to harm (NNH), which corresponds theoretically to the number of prescriptions needed with the CCB/clarithromycin combination, as opposed to CCB/azithromycin, to lead to one patient event. The overall NNH was 464 for AKI, whereas for those with underlying CKD, the NNH was only 95, suggesting a heightened risk in CKD, as may be expected. Notably, the authors highlight that appropriate dose reduction of clarithromycin was not commonly done in patients with CKD. Several sensitivity analyses confirmed findings from the primary analysis. First, they confirmed the finding in patients with available serum creatinine values to define AKI, eliminating the possibility of confounding by differential misclassification of administrative codes. Second, they showed dose-dependence of the effect with higher versus lower doses of clarithromycin. Finally, they demonstrated temporal specificity by finding no association when examining AKI 90 days before or 90 days after drug prescription. Interestingly, the risk of mortality also was substantially higher with clarithromycin than azithromycin coprescription with a CCB, with an NNH of 231. An earlier study⁹ from this same group found that clarithromycin compared to azithromycin, not restricted to coadministration with a CCB, also was associated with a higher risk of death, but not with AKI. The extent to which the clarithromycin-alone effect confounds the findings by Gandhi et al⁵ on AKI is not clear. Irrespective of this minor point, their findings are clinically significant, related to a

plausible biological and pharmacologic mechanism, and important from a public health and safety standpoint.

HOW DOES THIS STUDY COMPARE WITH PRIOR STUDIES?

Several case reports have been published on the occurrence of severe hypotension and shock in patients treated with a CCB and erythromycin, clarithromycin, or telithromycin.^{10–13} In a population-based, nested, case-crossover study, Wright et al¹⁴ found that older adults treated with a CCB had a higher risk of hypotension or shock requiring hospital admission when coprescribed erythromycin or clarithromycin, as compared to azithromycin. The Ontario group led by Dr Garg also has shown in a population-based study by Patel et al¹⁵ that coprescription of a statin with clarithromycin or erythromycin was associated with a higher risk for hospitalization with rhabdomyolysis or AKI.

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

The study by Gandhi et al⁵ highlights the importance of developing systems-level interventions to prevent adverse drug events, particularly in the context of kidney disease. Some computerized prescription support systems have been implemented and studied in patients with kidney disease.^{16,17} One study examined the use of a computerized provider order entry to provide decision support regarding contraindicated or high-toxicity medications in patients with AKI and found that implementation resulted in a significant increase in modification or discontinuation of potentially toxic medications.¹⁸

Computerized support systems also may assist in avoiding drug interactions and toxicity in complex medical patients. SFINX (Swedish, Finnish, Interaction X-referencing) is a drug-drug interaction electronic database that can be integrated into the electronic medical record. Andersson et al¹⁹ found that implementation of SFINX reduced the number of potentially serious drug-drug interactions after integration of the database into electronic health records in a primary care setting. IM-Pharma, another electronic screening system to detect drug-drug interactions, also was shown to reduce the occurrence of inappropriate prescriptions with drug-drug interactions.²⁰ InterMED-Rx is a software program designed to identify CYP450 drug-drug interactions; its implementation was reported to identify elderly patients at risk for drug-drug interactions.²¹

Even with sophisticated software programs to identify adverse drug events in real time, physicians who prescribe medications must heed the warnings and act on them. As electronic clinical decision support systems proliferate, physicians are receiving increasing numbers of alerts, leading in many instances to “alert fatigue.”^{22,23} Therefore, clinicians, researchers, and information technology leaders also must identify barriers to the effective implementation of clinical decision supports and devise systems-level interventions to overcome them. With effective clinical decision support systems in place, many of the AKI admissions included in the database examined by Gandhi et al⁵ may have been and should in the future be avoided.

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