Liver injury in the elderly due to fluoroquinolones: Should these drugs be avoided?

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See related research article by Paterson and colleagues on page 1565 and at www.cmaj.ca/lookup/doi/10.1503/cmaj.111823

A clinician may be faced with the question "What is the risk of drug-induced liver injury if I prescribe drug *X* compared with drug *Y*?" In a related *CMAJ* article, Paterson and colleagues report a significantly higher risk of drug-induced liver injury with the use of levofloxacin and moxifloxacin compared with clarithromycin, ciprofloxacin or cefuroxime.[1] However, residual bias and the rarity of hepatotoxicity for all of the agents studied means that the choice between these antibiotics remains a matter of clinical need rather than hedging the risk of toxicity. In other words, one should still choose the antibiotic most likely to cover the infection and worry less about the liver.

Nevertheless, if a clinician has narrowed the choice to 2 or 3 drugs, he or she may just want to know which drug is safest and by how much. In registries, clarithromycin accounts for a low proportion of cases of hepatotoxicity (1.1% of 4680 cases),[2] whereas fluoroquinolones are more frequently involved (3.2% of 1069 cases).[3] However, these studies cannot yield accurate incidence rates owing to the lack of data on community exposure to antibiotics. Population-based studies can yield crude incidence data: based on reports of adverse events to the US Food and Drug Administration, 6.6 cases of severe hepatotoxicity per 10 million prescriptions were reported for moxifloxacin, 2.1 cases per 10 million were reported for levofloxacin and 1.1 cases per 10 million were reported for clarithromycin.[4] However, these data suffer from underreporting and varying diagnostic validity.[5]

Paterson and colleagues should be commended for their novel approach of employing a nested case–control design to estimate the relative odds of drug-induced liver injury using clarithromycin as the reference drug, thus bypassing the need for accurate incidence data. By doing so, the authors argue that these cases of hepatotoxicity are subject to the same biases and should thus yield useful odds ratios relative to each other, even though the estimates of absolute incidence may be inaccurate. The authors wisely chose these antibiotics because they have similar indications, and a clinician may be faced with choosing between each of them. Although the pathophysiology of liver toxicity from fluoroquinolones and macrolides is unclear, both have similarly quick onset of liver injury after the start of treatment and a propensity for immunoallergic features (e.g., rash, fever). These similarities may make the accuracy of diagnosing drug-induced liver injury in their study similar between agents.

However, there are important potential confounders besides those mentioned by the authors.[1] The study is prone to such confounding because the accuracy of the coding used to diagnose drug hepatotoxicity is assuredly much lower than the 95% positive predictive value quoted for cases of acetaminophen hepatotoxicity.[6] Because of acetaminophen's stereotypic injury pattern, epidemiology (sex, age, history of overdose) and diagnostic drug levels, diagnosis of acetominophen-induced liver injury is much clearer than idiosyncratic drug hepatotoxicity. None of these characteristics exist for the idiosyncratic reactions studied by Paterson and colleagues.

The study is vulnerable to biases created by the choice of antibiotic, which differentially affects the accuracy of diagnosing drug-induced liver injury between groups. For example, clarithromycin interacts strongly with the widely used vinca alkaloids, leading oncologists to avoid clarithromycin in certain patients. Vinca alkaloids are often used for malignancies that

Key points

- The risk of severe drug-induced liver injury is probably higher with moxifloxacin and levofloxacin compared with clarithromycin, cefuroxime and ciprofloxacin, but residual confounders hinder accurate estimates of how much higher.
- Although the relative odds of severe drug-induced liver injury may be higher for fluoroquinolones, the absolute risk of severe drug-induced liver injury for any of the antibiotic agents studied is very low.
- Until these observations are independently validated and rates of injury are found to be significantly higher for fluoroquinolones, we think that clinicians should choose the most efficacious antibiotic rather than try to avoid a very uncommon drug-induced liver injury.

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can invade the liver, leading to injury. Although both clarithromycin and fluoroquinolones can cause severe arrhythmias (e.g., torsades de pointes), the much higher risk with clarithromycin[7] may have led clinicians to favour fluoroquinolones in patients with severe heart disease. In our experience, drug-induced liver injury is particularly difficult to diagnose in people with cancer or heart failure owing to competing diagnoses such as cancer infiltration, multiple hepatotoxic agents, cholestasis of sepsis and ischemic or congestive liver injury. Thus, the fluoroquinolone group was prone to being enriched with patients in whom other diagnoses may have caused or contributed to liver injury, thereby leading to a possible overestimation of drug-induced injury.

Although the authors tried admirably to control for comorbidities and overall baseline health, clinicians are still more likely to choose moxifloxacin or levofloxacin over clarithromycin, cefuroxime or ciprofloxacin in patients who are immunocompromised and who may move quickly to sepsis.

All of these biases are particularly pertinent to this cohort, with a high mortality of 61.1%,[1] suggesting that comorbidities such as cancer, heart failure and sepsis contributed substantially to the poor outcomes of hepatotoxicity the authors saw. By comparison, patients admitted to hospital primarily for drug-induced liver injury have a mortality of 23%.[8] Hence, sensitivity analyses adjusting for diagnoses relating to cardiac, immunodeficiency and cancer would have been helpful.

However, the largest barrier preventing this study from persuading a clinician to choose one antibiotic over another is the low absolute risk of liver injury for any of the drugs studied. If the absolute incidence is between 1 and 6 per 10 million prescriptions, as previously reported,[4] then a doubling of odds for a fluoroquinolone compared with clarithromycin is still a very low risk. The risk remains low even if we accept the higher rates of 3.95 to 8.62 per 100 000 exposures reported by Paterson and colleagues,[1] which they admit may be overestimates. Therefore, consideration of comparative risk of hepatotoxicity should be superseded by other factors such as patterns of antibiotic resistance, type of infection, severity of illness and comorbidities. Indeed, it is telling that hepatologists often reach for fluoroquinolones when caring for patients with cirrhosis, in whom the chance of a suboptimally treated infection causing harm far outweighs any increased risk of drug-induced liver injury.[9,10] For similar reasons, and because the onset of liver injury is often quick and unpredictable, monitoring liver enzymes during treatment with moxifloxacin or levofloxacin is not advised.

For the clinician, there may be rare instances in which it is truly a toss-up as to which antibiotic is better for treating an infection. In such cases, based on the data from this and previous studies, clarithromycin may be slightly favoured. However, basing a decision on these data ahead of much more important factors would be misguided. Until these observations are independently validated and rates of injury are found to be significantly higher for fluoroquinolones, we think that clinicians should choose the most efficacious antibiotic rather than try to avoid an uncommon drug-induced liver injury.

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