The risk of hypotension following co-prescription of macrolide antibiotics and calcium-channel blockers

Alissa J. Wright MD, Tara Gomes MHSc, Muhammad M. Mamdani PharmD MPH, John R. Horn PharmD, David N. Juurlink MD PhD

Abstract

Background: The macrolide antibiotics clarithromycin and erythromycin may potentiate calcium-channel blockers by inhibiting cytochrome P450 isoenzyme 3A4. However, this potential drug interaction is widely underappreciated and its clinical consequences have not been well characterized. We explored the risk of hypotension or shock requiring hospital admission following the simultaneous use of calcium-channel blockers and macrolide antibiotics.

Methods: We conducted a population-based, nested, case-crossover study involving people aged 66 years and older who had been prescribed a calcium-channel blocker between Apr. 1, 1994, and Mar. 31, 2009. Of these patients, we included those who had been admitted to hospital for the treatment of hypotension or shock. For each antibiotic, we estimated the risk of hypotension or shock associated with the use of a calcium blocker using a pair-matched analytic approach to contrast each patient's exposure to each macrolide antibiotic (erythromycin, clarithromycin or azithromycin) in a seven-day risk interval immediately before admission to hospital and in a seven-day control interval one month earlier.

Results: Of the 7100 patients admitted to hospital because of hypotension while receiving a calcium-channel blocker, 176 had been prescribed a macrolide antibiotic during either the risk or control intervals. Erythromycin (the strongest inhibitor of cytochrome P450 3A4) was most strongly associated with hypotension (odds ratio [OR] 5.8, 95% confidence interval [CI] 2.3–15.0), followed by clarithromycin (OR 3.7, 95% CI 2.3–6.1). Azithromycin, which does not inhibit cytochrome P450 3A4, was not associated with an increased risk of hypotension (OR 1.5, 95% CI 0.8–2.8). We found similar results in a stratified analysis of patients who received only dihydropyridine calcium-channel blockers.

Interpretation: In older patients receiving a calcium-channel blocker, use of erythromycin or clarithromycin was associated with an increased risk of hypotension or shock requiring admission to hospital. Preferential use of azithromycin should be considered when a macrolide antibiotic is required for patients already receiving a calcium-channel blocker.

Competing interests: Muhammad Mamdani has worked as a consultant for Pfizer, Novartis and Jansen-Ortho. John Horn has worked as a consultant for Merck Consumer Care, and is the author of several books on the subject of drug interactions. No competing interests were declared by the other authors.

This article has been peer reviewed.

Correspondence to: Dr. David Juurlink, dnj@ices.on.ca

***CMAJ* 2011. DOI:10.1503/cmaj.100702**

Macrolides (erythromycin, clarithromycin and azithromycin) are the most widely prescribed antibiotics, with over 66 million prescriptions dispensed in 2008 in the United States alone.[1] Although they are generally well tolerated, they can provoke drug interactions by several mechanisms. The most well-studied of these involves the inhibition of the cytochrome P450 enzymes involved in drug metabolism, particularly cytochrome P450 isoenzyme 3A4. This enzyme plays an important role in the metabolism of many medications. It is strongly inhibited by clarithromycin and erythromycin but not by azithromycin.[2,3] In the presence of an inhibitor of this isoenzyme, drugs that require cytochrome P450 3A4 for their metabolism will accumulate, potentially leading to toxicity.[4,5]

Cytochrome P450 3A4 has many substrates of clinical relevance, but the calcium-channel blockers are of particular importance. These drugs are widely used for several chronic conditions, including hypertension and coronary artery disease. They are the ninth most commonly prescribed class of medications in the United States, with almost 90 million prescriptions dispensed in 2008.[1] Moreover, they are all substrates for cytochrome P450 3A4.[6,7] Erythromycin was shown to increase felodipine levels by about 300% in 12 patients,[8] and several case reports have described significant cardiovascular toxicity in patients receiving a calcium-channel blocker in combination with erythromycin or clarithromycin.[9–13] In contrast, no reports describe

such toxicity in patients given azithromycin, which is consistent with the observation that it does not inhibit cytochrome P450 3A4.[14]

Given the popularity of macrolides and calcium-channel blockers, millions of patients worldwide are likely exposed to this drug combination each year. However, the potential interaction between these drugs is not widely appreciated, and no rigorous studies describe the clinical consequences. We analyzed the health care records of more than 1.5 million older individuals to characterize the clinical consequences of macrolide use among patients who were taking a calcium-channel blocker.

Methods

Data sources

We conducted a population-based study of residents aged 66 years or older in the province of Ontario. Prescription drug records were obtained from the Ontario Drug Benefit Claims Database, and information on hospital admissions was collected using the Canadian Institute for Health Information's Discharge Abstract Database. Demographic information was derived from the Registered Persons Database, which contains an entry for each resident of Ontario who has been issued a health card. Finally, the Ontario Health Insurance Plan Database provided information regarding claims for physician services. These databases are linked anonymously using encrypted health card numbers. They are routinely used to study drug safety, including the consequences of drug interactions.[15–18] This study was approved by the Research Ethics Board of the Sunnybrook Health Sciences Centre.

Identification of patients and outcomes

We established a cohort of patients prescribed a single calcium-channel blocker (verapamil, diltiazem, nifedipine, amlodipine or felodipine) between Apr. 1, 1994, and Mar. 31, 2009. For each patient, we defined a period of continuous use of a calcium-channel blocker beginning with the first prescription for the drug after the patient's 66th birthday, as has been done in previous studies.[15,16,18] Continuous use of calcium-channel blockers was defined as the receipt of a refill for the drug within 180 days of the date of the previous prescription. Patients were deemed to have stopped their therapy if more than 180 days elapsed between prescriptions. In this situation, patients were followed for an additional 60 days from the date of their last prescription to identify any events that may have precipitated cessation. Observation ended with admission to hospital for treatment of an outcome of interest, death, discontinuation of therapy or a switch to a different calcium-channel blocker, whichever occurred first.

We excluded patients during their first year of eligibility for coverage of prescription medications under the Ontario Drug Benefit Program (i.e., those aged 65 years) to avoid incomplete medication records. Patients who had prescriptions for more than one macrolide in the 30 days before admission to hospital were also excluded.

In the primary analysis, we identified patients in the cohort who were admitted to hospital for treatment of either hypotension or shock according to the following International Classification of Diseases codes (both the 9th and 10th revisions were used): ICD-9 458.0, 458.1, 458.9, 785.50, 785.51 and 785.59; and ICD-10 I95.0, I95.1, I95.2, I95.8, I95.9, R57.0, R57.1, R57.8 and R57.9. We examined data only for patients in whom hypotension was present at the time of admission to hospital. The date of admission to hospital served as the reference date for all analyses. Only the first instance of each outcome was examined for each patient.

Design and analysis

We used the case-crossover design to avoid potential concerns about unresolved confounding. This technique allows one to assess the brief change in risk associated with a transient exposure.[19] Under this design, each person serves as his or her own control; consequently, confounding due to age, sex and other fixed patient factors is extinguished. We used the pair-matched analytic approach to contrast exposure to each macrolide in a seven-day risk period immediately before admission to hospital with a seven-day control period one month earlier. The case-crossover design was nested in the cohort of patients receiving a calcium-channel blocker.

For each of the macrolide antibiotics, we estimated the risk of hypotension during treatment with a calcium-channel blocker based on the odds ratio, contrasting exposure during the risk period against exposure during the control interval. The possible role of chance was assessed using the McNemar test. The threshold for statistical significance was set at a two-tailed type I error rate of 0.05.

Results

We identified 999 234 patients who were receiving a single calcium-channel blocker during the period under investigation. The median age was 71 years (interquartile range [IQR] 67–78 years). Within this cohort, 7100 patients were admitted to hospital for the treatment of hypotension (Table 1). Slightly more than half of these patients were

women, the median age was 77 years (IQR 72–83) and 176 patients had received a macrolide during either the risk or control intervals.

We found a strong association between erythromycin use and admission to hospital for the treatment of hypotension (odds ratio [OR] 5.8, 95% confidence interval [CI] 2.3–15.0), along with a marginally lower but significant risk associated with the use of clarithromycin (OR 3.7, 95% CI 2.3–6.1; Table 2). In contrast, we found no such association with azithromycin use (OR 1.5, 95% CI 0.8–2.8). We found similar results in a stratified analysis of patients receiving one of the dihydropyridine calcium-channel blockers (nifedipine, amlodipine or felodipine; Table 3).

Interpretation

Among older patients receiving calcium-channel blockers, the use of erythromycin and clarithromycin was associated with a markedly increased short-term risk of admission to hospital, whereas azithromycin use was not. These findings are consistent with previous case reports and with the known pharmacology of these drugs (erythromycin and clarithromycin both inhibit cytochrome P450 3A4, whereas azithromycin does not). They therefore have considerable clinical relevance. Calcium-channel blockers and macrolide antibiotics are among the most widely prescribed medications in Canada, and their interactions are both dangerous and greatly underappreciated. When a macrolide antibiotic is necessary, the interaction is easily avoided if azithromycin is given to patients who are already receiving a calcium-channel blocker.

Limitations

Several limitations of this study merit emphasis. We were unable to quantify medication adher-

Table 1: Characteristics of 7100 patients taking a calcium-channel blocker who were admitted to hospital for the treatment of hypotension or shock

Variable	No. (%) of patients* *n = 7100*	Variable	No. (%) of patients* *n = 7100*
Age, yr, median (IQR)	77 (72–83)	Myocardial infarction in the last 2 years	1169 (16.5)
65–74	2631 (37.1)	Heart failure in the last 2 years	1208 (17.0)
75–84	3057 (43.1)	Medication use in the last 100 days	
≥ 85	1412 (19.9)	P-glycoprotein inhibitors†	4762 (67.1)
No. of years using a CCB, median (IQR)	2 (1–5)	ACE inhibitor	3256 (45.9)
Type of CCB		NSAID	2724 (38.4)
Diltiazem	2838 (40.0)	Other diuretic	2547 (35.9)
Verapamil	566 (8.0)	β-adrenergic antagonist	2510 (35.4)
Nifedipine	1379 (19.4)	Statin	2182 (30.7)
Amlodipine	2101 (29.6)	Thiazide	1371 (19.3)
Felodipine	216 (3.0)	Digoxin	1117 (15.7)
Sex, male	3349 (47.2)	CYP3A4 inhibitors‡	886 (12.5)
Resident in long-term care facility	212 (3.0)	CYP3A4 inducers§	201 (2.8)
Income quintile		Angiotensin receptor blocker	696 (9.8)
Missing data	132 (1.9)	Spironolactone	399 (5.6)
1 (lowest)	1685 (23.7)	Charlson Comorbidity Index	
2	1618 (22.8)	0	1210 (17.0)
3	1304 (18.4)	1	1240 (17.5)
4	1195 (16.8)	≥ 2	2928 (41.2)
5 (highest)	1166 (16.4)	No admission to hospital	1722 (24.3)
No. of admissions to hospital in the last year, median (IQR)	0 (0–1)	Renal disease in the last year	562 (7.9)
No. of medications prescribed in the last 100 days, median (IQR)	12 (9–17)		

Note: ACE = angiotensin converting enzyme, CCB = calcium-channel blocker, CYP3A4 = cytochrome P450 isoenzyme 3A4, IQR = interquartile range, NSAID = nonsteroidal anti-inflammatory drug.
*Unless otherwise stated.
†Amiodarone, atorvastatin, carvedilol, itraconazole, nelfinavir, ritonavir and saquinavir.
‡Amiodarone, aprepitant, ciprofloxacin, delavirdine, fluconazole, imatinib, indinavir, itraconazole, nefazodone, nelfinavir, norfloxacin, ritonavir, saquinavir, telithromycin and voriconazole.
§Carbamazepine, efavirenz, nevirapine, phenobarbital, phenytoin and pioglitazone.

Table 2: Odds of admission to hospital for the treatment of hypotension or shock associated with recent exposure to macrolide antibiotics among patients already taking a calcium-channel blocker*

Antibiotic	Use during risk interval	Use during control interval	*p* value	OR (95% CI)
Erythromycin	30	6	< 0.001	5.80 (2.25–14.98)
Clarithromycin	77	23	< 0.001	3.70 (2.26–6.06)
Azithromycin	24	16	0.21	1.50 (0.8–2.82)

Note: CI = confidence interval, OR = odds ratio.
*Risk interval = seven days before hospital admission; control interval = seven-day period one month before admission.

Table 3: Odds of admission to hospital for the treatment of hypotension or shock and use of macrolide antibiotics among patients receiving a dihydropryidine calcium-channel blocker*

Antibiotic	Use during risk interval	Use during control interval	*p* value	OR (95% CI)
Erythromycin	17	≤ 5†	0.01	3.40 (1.25–2.78)
Clarithromycin	51	12	< 0.001	4.25 (2.23–7.97)
Azithromycin	12	10	0.67	1.20 (0.52–2.78)

Note: CI = confidence interval, OR = odds ratio.
*Nifedipine, felodipine or amlodipine.
†Cells with five or fewer observations are suppressed in accordance with institutional privacy policy.

ence, or type and severity of infection, and the accuracy of diagnostic codes for hypotension has not been validated. Hypotension has multiple possible causes, and some instances of hypotension may have reflected the response to infection rather than the consequence of a drug interaction. We did not have sufficient statistical power to explore the outcome of bradycardia, which, along with hypotension, might be expected in patients receiving verapamil or diltiazem. Finally, we were unable to characterize the magnitude of interaction for each of the calcium-channel blockers. This is important because the inhibitory effect of erythromycin and clarithromycin on cytochrome P450 3A4 would be expected to result in a greater relative increase in the level of calcium-channel blockers that undergo greater presystemic elimination, most notably felodipine.[20] However, these limitations apply equally to all macrolide antibiotics, including azithromycin, the inclusion of which lessens the role of confounding in our analyses. These limitations are unlikely to explain the differential risk seen with clarithromycin and erythromycin, which is biologically plausible and predicted by the pharmacology of these drugs.

Conclusion

We found that older patients taking a calcium-channel blocker were at increased risk of admission to hospital for the treatment of hypotension or shock following the use of clarithromycin or erythromycin. Our findings highlight the consequences of an underappreciated yet avoidable drug interaction involving medications used by millions of patients every year. Clinicians should be aware of the potential interaction between these drugs. When a macrolide is required, preferential use of azithromycin should be considered in patients already receiving a calcium-channel blocker.

References

1. IMS Health. *Top therapeutic classes by dispensed prescriptions*. Thetford Center (VT): MarketingCharts. Available: www.marketingcharts.com/topics/us-prescription-drug-sales-grow-slowly-hydrocodone-most-prescribed-8462/ims-top-15-us-therapeutic-classes-dispensed-prescriptions-2008jpg/ (accessed 2009 July 1).
2. Periti P, Mazzei T, Mini E, et al. Pharmacokinetic drug interactions of macrolides. *Clin Pharmacokinet* 1992;23:106-31.
3. Westphal JF. Macrolide-induced clinically relevant drug interactions with cytochrome P-450A (CYP) 3A4: an update focused on clarithromycin, azithromycin and dirithromycin. *Br J Clin Pharmacol* 2000;50:285-95.
4. Dresser GK, Spence JD, Bailey DG. Pharmacokinetic–pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. *Clin Pharmacokinet* 2000;38:41-57.
5. Zhou S, Chan E, Li X, et al. Clinical outcomes and management of mechanism-based inhibition of cytochrome P450 3A4. *Ther Clin Risk Manag* 2005;1:3-13.
6. Sica DA. Interaction of grapefruit juice and calcium channel blockers. *Am J Hypertens* 2006;19:768-73.
7. Dorne JL, Walton K, Renwick AG. Human variability in CYP3A4 metabolism and CYP3A4-related uncertainty factors for risk assessment. *Food Chem Toxicol* 2003;41:201-24.
8. Bailey DG, Bend JR, Arnold JM, et al. Erythromycin–felodipine interaction: magnitude, mechanism, and comparison with grapefruit juice. *Clin Pharmacol Ther* 1996;60:25-33.
9. Liedholm H, Nordin G. Erythromycin–felodipine interaction. *DICP* 1991;25:1007-8.
10. Kaeser YA, Brunner F, Drewe J, et al. Severe hypotension and bradycardia associated with verapamil and clarithromycin. *Am J Health Syst Pharm* 1998;55:2417-8.

11. Steenbergen JA, Stauffer VL. Potential macrolide interaction with verapamil. *Ann Pharmacother* 1998;32:387-8.
12. Goldschmidt N, Azaz-Livshits T, Gotsman, et al. Compound cardiac toxicity of oral erythromycin and verapamil. *Ann Pharmacother* 2001;35:1396-9.
13. Geronimo-Pardo M, Cuartero-del-Pozo AB, Jimenez-Vizuete JM, et al. Clarithromycin-nifedipine interaction as possible cause of vasodilatory shock. *Ann Pharmacother* 2005;39:538-42.
14. Pai MP, Graci DM, Amsden GW. Macrolide drug interactions: an update. *Ann Pharmacother* 2000;34:495-513.
15. Juurlink DN, Mamdani M, Kopp A, et al. Drug–drug interactions among elderly patients hospitalized for drug toxicity. *JAMA* 2003;289:1652-8.
16. Park-Wyllie LY, Juurlink DN, Kopp A, et al. Outpatient gatifloxacin therapy and dysglycemia in older adults. *N Engl J Med* 2006;354:1352-61.
17. Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ* 2009;180:713-8.
18. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004;351:543-51.
19. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol* 1991;133:144-53.
20. Kirsten R, Nelson K, Kirsten D, et al. Clinical pharmacokinetics of vasodilators. Part I. *Clin Pharmacokinet* 1998;34:457-82.

Affiliations: From the Departments of Medicine (Wright, Juurlink) and Health Policy, Management and Evaluation (Mamdani), University of Toronto, Toronto, Ont.; St. Michael's Hospital, Applied Health Research Centre, Li Ka Shing Knowledge Institute (Mamdani), Toronto, Ont.; the Departments of Pharmacy and Pharmacy Services (Horn), University of Washington, Seattle, Wash.; the Sunnybrook Research Institute (Juurlink), Toronto, Ont.; and the Institute for Clinical Evaluative Sciences (Mamdani, Gomes, Juurlink), Toronto, Ont.

Contributors: David Juurlink is the study guarantor and assumes responsibility for the integrity of the data and the accuracy of the analysis. Alissa Wright, Tara Gomes, Muhammad Mamdani, John Horn and David Juurlink contributed to the concept and design of the study. Alissa Wright and David Juurlink drafted the manuscript. Tara Gomes performed the analyses. All of the authors contributed to the interpretation of the analysis, revised the manuscript and approved the version submitted for publication.

Funding: This study was supported by the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care. The study was supported in part by the Ontario Drug Innovation Fund, which had no role in the design, analysis, conduct or reporting of the study. The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario Ministry of Health and Long-Term Care is intended or should be inferred.

Acknowledgements: The authors thank Brogan Inc., Ottawa, Ont., for use of its Drug Product and Therapeutic Class Database, and Ashif Kachra, Jill Tomac and Chelsea Hellings for assistance with manuscript preparation.

Presented in part at the Canadian Society of Internal Medicine Annual Scientific Meeting in Vancouver, British Columbia, Oct. 30, 2010.