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SHORT COMMUNICATION

Clinical Hypotension with Co-prescription of Macrolide Antibiotics and Calcium-Channel Blockers in Haemodialysis Patients: A Retrospective Chart Review

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Abstract

Background Macrolide antibiotics inhibit the cytochrome p450 enzyme system, which metabolizes calcium-channel blockers. This may result in a clinically significant interaction, causing hypotension in patients co-prescribed these two drugs. Since these drugs are frequently used in the haemodialysis population, we studied the effect of their co-prescription on actual blood pressure.

Methods A retrospective chart review of all haemodialysis patients was conducted to identify patients co-prescribed a macrolide and a dihydropyridine calcium-channel blocker. Blood pressure measurements before and during the macrolide co-prescription were abstracted and compared using a student's *t* test.

Results We identified 154 haemodialysis patients concurrently prescribed a macrolide antibiotic and a dihydropyridine calcium-channel blocker. There was no significant difference in episodes of intra-dialytic hypotension or actual blood pressure measurements in the period before macrolide co-prescription and the period during macrolide co-prescription.

Conclusion In contrast to hospitalized patients receiving dihydropyridine calcium-channel blockers, concurrent administration of a macrolide antibiotic for infection did not result in hypotension in haemodialysis outpatients. Further research should be undertaken before a change in clinical practice against their co-prescription is considered.

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1 Background

Macrolide antibiotics, particularly erythromycin and clarithromycin, are known to inhibit the cytochrome p450 (CYP) 3A system and may therefore interact with other CYP3A-metabolizing drugs [1]. Since the CYP3A4 system is also responsible for metabolism of calcium-channel blockers, clarithromycin co-prescription might lead to uncontrolled vasodilatation, thus leading to hypotension [2]. Wright et al. [3] recently reported that use of erythromycin and clarithromycin, but not azithromycin, was associated with an increased risk of hypotension or shock requiring admission to hospital in older patients receiving a calcium-channel blocker. Azithromycin is known to interfere poorly with the CYP system in vitro, in comparison with erythromycin and clarithromycin, which may explain this differential interaction [1, 4]. Other groups have subsequently urged caution with co-prescription of macrolide antibiotics and calcium-channel blockers [5].

Calcium-channel blockers are widely prescribed for patients with hypertension [6], and they have been reported to be the most commonly used antihypertensive class in haemodialysis patients [7]. Haemodialysis patients are also particularly prone to episodes of hypotension related to rapid changes in blood volume [8]. Infections and antibiotic use are also quite common in haemodialysis patients, with a reported annual incidence of 32 % of such patients

requiring hospitalization [9]. In haemodialysis patients, blood pressure measurements are taken pre-dialysis, post-dialysis and every 30 minutes intra-dialysis, and are logged in the electronic patient record. Given the availability of such accurate electronic data on blood pressure and medication use in haemodialysis patients, we evaluated the risk of concurrent macrolide and calcium-channel blocker use on the incidence of hospitalization for hypotension or shock. Additionally, since haemodialysis patients frequently experience hypotension during and after the haemodialysis procedure [8, 10] and may be more seasoned to the accompanying symptoms, we assessed whether the combination of macrolides and calcium-channel blockers was associated with a clinically significant decrease in blood pressure in comparison with the period before initiation of this therapy. Lastly, we also compared blood pressure measurements for patients who received clarithromycin versus azithromycin.

2 Methods

A retrospective chart review of all haemodialysis patients at our tertiary care centre was conducted for the period Jan 2003 to July 2010, using the Nephrocare (Fresenius Medical Care, Bad Homburg, Germany) electronic medical record. In our haemodialysis program, medication reconciliation is done every month, every time a patient has a hospitalization event, and when a new prescription is provided to the patient. It is done by a hemodialysis nurse, which is reviewed and confirmed by the treating nephrologist. Patients who were prescribed a calcium-channel blocker and a macrolide antibiotic were identified from the electronic records. These charts underwent manual review to confirm co-prescription of the two classes of medication. Data for demographics and blood pressure measurements were then abstracted. Diabetic status was recorded, since diabetes is the most common cause of kidney failure in this population and these patients have an inadequate hemodynamic response to changes in volume status (as happens frequently on haemodialysis) and have a greater propensity for clinical hypotension. The systolic and diastolic blood pressure measurements taken at the initiation of dialysis ('pre-dialysis') and at the termination of dialysis ('post-dialysis') were abstracted. Blood pressure measurements are taken every 30 min during the haemodialysis procedure, as well as when the patient is symptomatic. The lowest systolic blood pressure recorded during dialysis was also abstracted. In addition, blood pressure measurements for the week prior to the start of macrolide treatment were recorded. Intra-dialytic hypotension was defined as a decrease in systolic blood pressure of $\geq$20 mmHg or a decrease in mean arterial pressure by 10 mmHg during dialysis, associated with clinical events and need for nursing interventions [10, 11]. Chi-squared and student's *t* tests were used to compare event rates and blood pressure measurements between patients receiving clarithromycin and those receiving azithromycin, as well as event rates and blood pressure measurements 1 week prior to and during co-prescription. All analysis was conducted with JMP software (version 8.0.1; SAS Inc., Cary, NC, USA). A p value of <0.05 was considered significant. This chart review was approved by the institutional review board (the Ottawa Hospital Research Ethics Board). Patient consent was deemed to be unnecessary, since there was no direct patient contact and the data were collected from an administrative database.

3 Results

Our chart review identified 1,518 patients who ever received a calcium-channel blocker and 555 who ever received a macrolide antibiotic during the study period. Among the 217 patients who received both drugs sometime during the study period, we then identified 157 who were prescribed a macrolide while they were already taking a calcium-channel blocker (Fig. 1). Three patients who were on agents that could potentially induce the CYP system (two patients on rifampin and one patient on carbamazepine) were excluded from the analysis, thus 154 patients were included in the final analysis. The characteristics of these patients are presented in Table 1. Amlodipine was the most common calcium-channel blocker used (in 124 patients), followed by nifedipine (29 patients) and felodipine (only one patient). Azithromycin was used in 89 patients (57.8 %), and clarithromycin was used in the remaining 65 patients (2.2 %).

For the period of co-prescription of the two classes of medication, we did not observe any hospitalization for hypotension or shock among these 154 patients. There was no difference in any of the blood pressure measurements or in the incidence of intra-dialytic hypotension (as defined a priori) between the week prior to and during the week of co-prescription, either overall or when compared for azithromycin and clarithromycin separately (Tables 2 and 3).

We also did not find a significant difference in the incidence of intra-dialytic hypotension between the patients prescribed azithromycin and those prescribed clarithromycin (Table 3). We also failed to find a significant difference in either the systolic or diastolic blood pressure measured at different timepoints (pre-dialysis, post-dialysis and lowest intra-dialytic) between patients prescribed the two macrolides.

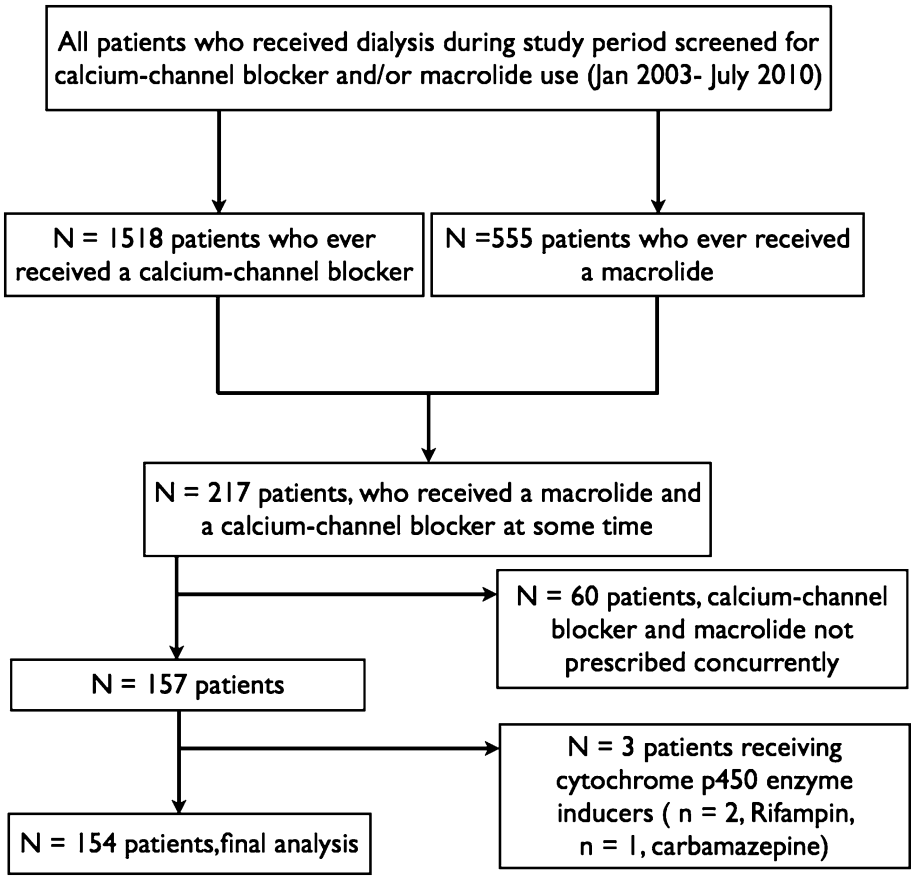

Fig. 1 Flow of patients included in the study

Table 1 Patient characteristics

Characteristic	All	Azithromycin	Clarithromycin
Patients (*n*)	154	89	65
Age [years; mean ± SD]	65.8 ± 14.4	66.3 ± 14.4	65.2 ± 14.6
Male gender [*n* (%)]	77 (50)	39 (43.8)	38 (58.5)
Diabetes [*n* (%)]	66 (42.9)	35 (39.3)	31 (47.7)
Calcium-channel blocker used [*n* (%)]			
Nifedipine	29 (18.8)	18 (80)	11 (16.9)
Amlodipine	124 (80.5)	71 (79.8)	55 (81.5)
Felodipine	1 (0.6)		1 (1.5)

SD standard deviation

4 Discussion

In contrast to a prior epidemiologic study [3], we failed to detect an effect of concurrent use of any macrolide with a calcium-channel blocker on blood pressure. The strength of our study was that we had detailed granular data on actual longitudinal blood pressure measurements while the patients were receiving a macrolide, as well as while they were off the macrolide. Haemodialysis patients have rapid changes in blood volume, and vasoconstriction and an increase in heart rate are the primary defence mechanisms to prevent hypotension in these patients [7, 8]. Hence this patient population would be more susceptible to the effects

Table 2 Blood pressure measurements 1 week prior to and during co-prescription of macrolides and calcium-channel blockers

Variable	1 week prior	During co-prescription	*p* value[a]
Intra-dialytic hypotension [*n* (%)]	100 (64.9)	97 (63.0)	0.62
Pre-dialysis SBP [mmHg; mean ± SD]	145.1 ± 24.5	146.3 ± 23.7	0.51
Post-dialysis SBP [mmHg; mean ± SD]	141.4 ± 24.8	142.8 ± 25.3	0.52
Lowest intra-dialytic SBP [mmHg; mean ± SD]	117.5 ± 22.8	119.5 ± 25.5	0.28
Intra-dialytic drop in SBP [mmHg; mean ± SD]	3.6 ± 21.2	3.5 ± 24.7	0.95

SBP systolic blood pressure, *SD* standard deviation

[a] *p* value using a paired *t* test

Table 3 Blood pressure measurement differences between azithromycin and clarithromycin 1 week prior to and during co-prescription with calcium-channel blockers

Variable	Azithromycin			Clarithromycin			*p* value[b]
	1 week prior	During co-prescription	*p* value[a]	1 week prior	During co-prescription	*p* value[a]	
Intra-dialytic hypotension [*n* (%)]	59 (66.3)	57 (64.0)	0.85	41 (63.1)	40 (61.5)	0.82	0.88
Pre-dialysis SBP [mmHg; mean ± SD]	146.4 ± 24.1	145.9 ± 22.0	0.82	143.3 ± 25.2	146.9 ± 25.9	0.20	0.80
Post-dialysis SBP [mmHg; mean ± SD]	142.4 ± 25.1	145.0 ± 26.6	0.33	140.1 ± 24.5	139.8 ± 23.4	0.92	0.19
Lowest intra-dialytic SBP [mmHg; mean ± SD]	117.3 ± 22.4	117.8 ± 24.9	0.77	118.0 ± 23.5	121.8 ± 26.3	0.18	0.34
Intra-dialytic drop in SBP [mmHg; mean ± SD]	3.9 ± 21.0	0.8 ± 25.1	0.28	3.2 ± 20.3	7.1 ± 23.9	0.24	0.12

SBP systolic blood pressure, *SD* standard deviation

[a] *p* value using a paired *t* test

[b] *p* value for the comparison between azithromycin and clarithromycin for measurements during co-prescription, using an unpaired *t* test

of uncontrolled vasodilatation that would occur with calcium-channel blockers. The failure to elicit more hypotension in the clarithromycin group compared with the azithromycin group thus argues against a clinically significant drug interaction in this population. Since neither amlodipine nor nifedipine is removed by haemodialysis [12, 13], it is unlikely that the difference between the outcomes of these two studies can be attributed to the presence of renal replacement therapy.

Our study did have certain limitations. An ideal study of drug interactions would need four groups of patients, and we had only two (patients on calcium-channel blockers alone, and patients on calcium-channel blockers and macrolides), with no data on the other two potential groups (patients on macrolides alone, and patients on neither drug) [14]. It is possible that we failed to detect a significant effect in our population because of the extremely low risk of a clinically significant interaction between dihydropyridine calcium-channel blockers and clarithromycin. It is also possible that we failed to detect a true difference (a type 2 error) because only 154 patients were studied; however, our actual population size was not much different from the 176 patients co-prescribed macrolides by Wright et al. [3] Additionally, results from the haemodialysis population may not be generalizable to the non-dialysis population. We also did not adjust for other co-morbid conditions which could potentially be effect modifiers, apart from diabetes. Lastly, in contrast to our study, all patients in the study by Wright et al. required admission to hospital, presumably because of the severity of their infection. There was no comparable cohort of patients who had exposure to both drugs but did not require admission to hospital, in direct contrast to our study. Thus one may consider the severity of infection as a possible determinant of the interaction between a macrolide and a calcium-channel blocker.

5 Conclusion

Altogether, in our cohort of haemodialysis patients, we were unable to confirm previous reports of a clinically significant interaction between macrolide antibiotics and calcium-channel blockers. Since prospective randomized trials are unlikely to be performed to definitely address whether a true interaction exists, we would encourage researchers with large administrative databases to also examine this question, as a larger data set may help to further clarify the true nature of any interaction between macrolide antibiotics and calcium-channel blockers.

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