Angiotensin axis antagonists increase the incidence of haemodynamic instability in dihydropyridine calcium channel blocker poisoning

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**ABSTRACT**

**Context:** Amlodipine, a dihydropyridine calcium channel blocker (CCB), is the leading cause of cardiovascular drug-related overdose deaths in the USA. In contrast, angiotensin-II receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEIs) cause minimal toxicity in overdose. ACEIs/ARBs are often combined with dihydropyridines in hypertension treatment. Co-ingested ARBs/ACEIs may significantly contribute to the toxicity of dihydropyridine, but this has not been investigated.

**Objective:** To investigate the clinical outcomes from dihydropyridine overdoses with ARBs/ACEIs versus dihydropyridine overdoses alone.

**Methods:** This was a retrospective study of patients reported to the New South Wales Poisons Information Centre (NSW PIC) and 3 toxicology units (Jan 2016 to Jun 2019) in Australia. Patients >14 years who took an overdose of dihydropyridines (amlodipine, felodipine, lercanidipine, nifedipine) were included. Concurrent overdoses with non-dihydropyridine CCBs, alpha-blockers and beta-blockers were excluded. Patient demographics, drugs exposure details, serial vital signs, treatments and outcome were collected.

**Results:** There were 100 patients. 68 took mixed overdoses of dihydropyridines with ARBs/ACEIs and 32 took single overdoses of dihydropyridines without ARBs/ACEIs. The mixed group had lower median nadir mean arterial pressures (62 vs 75 mmHg, p < 0.001), more frequently had hypotension (OR 4.5, 95%CI: 1.7–11.9) or bradycardia (OR 8.8, 95%CI: 1.1–70). Multivariable analysis indicated the mixed overdoses had an 11.5 mmHg (95%CI: 4.9–18.1) lower minimum systolic blood pressure (SBP) compared with the single group; other factors associated with a lower minimum SBP were higher doses [2.3 mmHg (95%CI: 1.1–3.5) lower per 10 defined daily doses] and younger age [2.2 mmHg (95%CI: 0.3–4.2) higher per decade]. A larger proportion of the mixed ingestion group received intravenous fluids (OR 5.7, 95%CI: 1.8–18.6) and antidotes and/or vasopressors (OR 2.9, 95%CI: 1.004–8.6).

**Conclusion:** Combined overdoses of dihydropyridines with ARBs/ACEIs caused more significant hypotension and required more haemodynamic support than overdoses of dihydropyridines alone.

**Introduction**

Dihydropyridine calcium channel blockers (CCBs) such as amlodipine, felodipine, lercanidipine and nifedipine are used as first-line treatment for essential hypertension [1]. In 2015, amlodipine was the fourth most commonly dispensed medication in Australia and the second most commonly prescribed antihypertensive medication by defined daily dose per day [2]. Dihydropyridine CCBs are perceived to be safer at therapeutic doses than non-dihydropyridine CCBs, such as verapamil and diltiazem, as they have more vascular selectivity and less negative chronotropy and inotropy [3]. Despite this, amlodipine is the leading contributor to cardiovascular drug related poisoning deaths (31.5%) in the USA [4]. Dihydropyridine overdose involves a loss of vascular selectivity [5,6] and a decrease in systemic vascular resistance to cause haemodynamic instability with hypotension and reflex tachycardia [7]. This may lead to vasodilatory shock [8,9].

Dihydropyridines are often prescribed in combination with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-II receptor blockers (ARBs). Combined therapy of dihydropyridines and ACEI/ARB may be superior to other first-line combinations such as beta-blockers with diuretics or ACEIs with diuretics in some patients [10,11]. In the renin-angiotensin-aldosterone system, ARBs block the Angiotensin (AT)-1 receptor of angiotensin-II and inhibit vasoconstriction [12] whilst ACEIs block angiotensin-converting enzyme (ACE) to inhibit the conversion of angiotensin I to angiotensin II, similarly leading to less vasoconstriction [13]. Overdoses of ARBs/ACEIs alone are relatively benign [14–17] and are rarely listed as the primary cause of poisoning deaths [4].
There is a paucity of evidence pertaining to the severity of a mixed dihydropyridine and ARB/ACEI overdose, with current literature predominately limited to case reports. A small number of case reports detail concurrent overdoses of dihydropyridines and an ARB/ACEI that have resulted in a prolonged and severe hypotension refractory to standard treatment with intravenous fluids, antidotes and vasopressors [8,9,18–24]. Therefore, this study aims to determine the clinical course of this poisoning in a larger cohort of patients, by comparing patients who had an overdose of a dihydropyridine with an ARB/ACEI, with patients who had an overdose of a dihydropyridine without an ARB/ACEI, in terms of haemodynamic stability, treatment requirements and patient outcomes.

Methods

Study design and setting

This was a multi-centre, retrospective study, with data collected from January 2016 to June 2019. Patients were retrospectively identified through the New South Wales Poisons Information Centre (NSW PIC), the South Eastern Area Toxicology Service (SEATS), the Princess Alexandra Toxicology Service (PATS) and the Hunter Area Toxicology Service (HATS) databases. These services collect data on drug exposures and doses prospectively from telephone consultations Australia-wide and admissions in local hospitals and the three toxicology units. In particular, the NSW PIC receives approximately half of Australia’s 200,000 poisons-related calls from the public and medical professionals [25]. This study received ethics approval provided by local Human Research Ethics Committees for NSW PIC (HREC/16/SCHN/71), HATS (LNR15/HNE/18), PATS (HREC/14/QPAH/308) and the SEATS (LNR/12/POWH/355).

Case identification

Patients >14 years who had orally ingested a dihydropyridine CCB over the maximum daily dose (amlodipine >10mg; felodipine >20mg; lercanidipine >20mg; nifedipine immediate release >80mg; nifedipine controlled release >120mg) were included. Patients were excluded if they had concurrently overdosed on a beta-blocker, an alpha blocker, verapamil or diltiazem, or if their medical records were sent with incomplete fluid, observation or treatment charts.

Data collection

Patients were separated into two groups; the first with a mixed overdose of a dihydropyridine with an ARB/ACEI, and the second with an overdose of a dihydropyridine without an ARB/ACEI. De-identified medical records were requested from hospitals Australia-wide for these patients. A custom-tailored REDCap abstraction form was created to standardise data collection for consistency and to reduce error. Demographical data and drug exposure details were collected. All vital sign observations during the admission (systolic blood pressure (SBP), diastolic blood pressure (DBP), calculated mean arterial pressure (MAP) and heart rate (HR)) were collected serially. Treatment, length of stay and final outcomes were also recorded. To standardise the overdose of different dihydropyridines, the number of defined daily doses (DDDs) ingested was calculated, as per the World Health Organization Collaborating Centre for Drugs Statistics Methodology [26]. Ten percent of patient charts were randomly selected and cross-checked by a second reviewer to confirm the accuracy and reliability of the initial data collection.

Outcomes

The two primary outcomes were the comparison of lowest SBP and the lowest MAP. Hypotension was defined as SBP <90 mmHg or DBP <60 mmHg or MAP <65 mmHg. Secondary outcomes included bradycardia, tachycardia, intravenous fluid requirement, decontamination, antidote and vasopressor requirements, intensive care unit admission and length of stay. Bradycardia was defined as a HR <60 bpm and tachycardia defined as HR >100 bpm.

Statistical analysis

The data were imported and analysed in Statistical Packages for the Social Sciences (SPSS; SPSS Inc., Chicago, IL, USA) and GraphPad Prism 8.1.2 (GraphPad Software Inc., San Diego, CA, USA). Normality was identified with Shapiro–Wilk test. The Mann–Whitney U test was used to compare non-parametric data between the two groups. Chi-squared test was used to compare categorical values, substituting Fisher’s exact test in comparisons when any cell size count was less than five. The Kaplan–Meier curves for time-to events (time to fluids, time to vasopressors and/or antidotes and time to discharge) were compared with the log rank test. Multiple linear regression was used to determine the correlation between co-ingestion of a dihydropyridine CCB and an ARB/ACEI vs. ingestion of a dihydropyridine CCB without an ARB/ACEI, age and DDD with lowest SBP and lowest MAP. A p-value <0.05 was deemed statistically significant.

Odds ratios (OR) are presented with a 95% confidence interval as a measure of association between mixed ingestions and binary outcomes. Multinominal logistic regression analysis was used to determine the adjusted odds ratio (aOR) to account for the influence of other covariates and/or factors.

Results

Patient demographics

A total of 223 cases were identified which satisfied the inclusion criteria. Forty-three patients were excluded due to a concurrent overdose of a beta-blocker, an alpha blocker, verapamil or diltiazem. Eighty patients were lost to follow up or had components of their records that were not sent to data collectors (Figure 1). A total of 100 patients were therefore included, with 68 having ingested a dihydropyridine with an
ARB/ACEI (mixed ingestion group), and 32 having ingested a dihydropyridine without an ARB/ACEI (single ingestion group). In terms of comorbid medical conditions, one patient in the single ingestion group and no patients in the mixed ingestion group had congestive cardiac failure. Two patients in the single ingestion group and five patients in the mixed ingestion group had ischaemic heart disease. Patient demographic and ingestion data are summarised in Table 1.

The proportion of amlodipine ingestions were significantly higher in the mixed group \((p = 0.008)\), whilst the proportion of lercanidipine ingestions were significantly higher in the single ingestion group \((p < 0.001)\). There was no significant difference in the proportion ingesting felodipine and nifedipine IR and ER. Forty-three patients from the mixed ingestion group (63%) ingested combination tablets containing dihydropyridines.

**Haemodynamic effects**

The mixed ingestion group had significantly lower nadirs for SBP and MAP during admissions (Table 2, Figure 2). The odds of hypotension were 4.5 times higher (95% CI: 1.7–12) in the mixed ingestion group, and this was statistically significant (Table 3). This remained significant after adjusting for age and DDD [adjusted odds ratio (aOR) = 3.9 (95% CI: 1.4–11)].

The mixed ingestion group had a significantly lower nadir for HR (Table 2). Bradycardia was more common in the mixed ingestion group [OR: 8.8 (95% CI: 1.1–70)], but when adjusted for age and DDD this difference was no longer statistically significant (Table 3). There was no difference in proportion of patients who experienced tachycardia.

In multivariable analysis, mixed ingestion, dose and age, but not gender, were associated with a lower nadir for SBP. With all other predictors kept constant, mixed overdoses had an 11.5 mmHg (95% CI: 4.9–18.1) lower minimum systolic blood pressure (SBP) compared with the single group; a lower minimum SBP was seen with higher doses [2.3 mmHg (95% CI: 1.1–3.5) lower per 10 daily defined doses] and younger age [SBP was 2.2 mmHg (95% CI: 0.3–4.2) higher per decade].
Treatment

A significantly larger proportion of the mixed ingestion group received intravenous fluids (aOR 4.9; Table 3). The volume of intravenous fluids received was also higher in the mixed ingestion group (4.0 L (IQR 2.4–5.6) vs. 3.5 L (IQR 1.9–5.0), p = 0.04). A significantly higher proportion of the mixed ingestion group received antidotes and/or vasopressors (OR 2.9, 95% CI: 1.004–8.6). However, this effect was not observed after adjustment for age, ingestion group and DDD (aOR 2.3, 95% CI: 0.73–7.4). The antidote and vasopressor agents received are detailed in Table 4. Log rank test of the Kaplan–Meier curve for time-to-fluids shows a significant difference between the two groups (p = 0.001). Log rank test of the Kaplan–Meier curve for time-to-vasopressors and/or antidotes just failed to show a significant difference between the two groups (p = 0.052; Figure 3).

A larger proportion of the single ingestion group received activated charcoal (p = 0.4) or was intubated (p = 0.7), but this was not statistically significant (Table 3). There were no cardiac arrests, seizures or strokes. There was no significant difference in median highest serum creatinine levels between the mixed and single ingestion groups (81 µmol/L (IQR 69–112.5) vs. 78 µmol/L (IQR 65–110), p = 0.78). There were no significant

| Table 3. Treatment and dichotomous haemodynamic outcomes. |
|-------------------|-------------------|------|-------------------|-------------------|-------------------|
| Parameter         | DHP CCB with ARB/ACEI (n = 68) | DHP CCB without ARB/ACEI (n = 32) | p Value | Odds ratio (95% CI) | Adjusted Odds ratio (95% CI) |
| Hypotensionb      | 58 (85%)           | 18 (56%)          | 0.002 | 4.5 (1.7–12)       | 3.9 (1.4–11)      |
| Bradycardiac      | 15 (22%)           | 1 (3%)            | 0.018 | 8.8 (1.1–70)       | 7.8 (0.97–63)     |
| Tachycardiad      | 33 (49%)           | 18 (56%)          | 0.47  | 0.73 (0.32–1.7)    | 0.73 (0.30–1.8)   |
| Number received activated charcoal | 7 (10%) | 5 (16%) | 0.44  | 0.62 (0.18–2.1)    | 0.78 (0.20–3.0)   |
| Number received intravenous fluids | 63 (93%) | 22 (69%) | 0.002 | 5.7 (1.8–19)       | 4.9 (1.5–16)      |
| Number received antidote or inotropes | 24 (35%) | 5 (16%) | 0.043 | 2.9 (1.004–8.6)    | 2.3 (0.7–7.4)     |
| Number of ICU admissions | 4 (6%) | 3 (9%) | 0.68  | 0.60 (0.13–2.9)    | 0.51 (0.094–2.7)  |
| Length of stay (days) | 1.3 (IQR 0.7–2.2) | 0.9 (IQR 0.5–1.6) | 0.10  | –                 | –                 |
| Deaths            | 0                 | 0                 | –     | –                 | –                 |

DHP: dihydropyridine.

*Adjusted for age, group and DDD.

bHypotension defined if SBP < 90 mmHg or DBP < 50 mmHg.

Bradycardia defined for heart rate < 60 bpm.

tachycardia defined for heart rate > 100 bpm.

Bold values represent statistically significant values.
differences in incidence of systemic symptoms between the two groups (Table 5). The three patients who developed pulmonary oedema in the mixed ingestion group, received 3 L, 6 L and 9 L of intravenous fluids respectively.

All patients survived and were discharged. There was no significant difference in length of stay between the two groups ($p = 0.1$; Table 3). Log rank test of the Kaplan–Meier curves for time-to-discharge (Figure 4) showed no significant difference between the two groups ($p = 0.3$).

**Discussion**

Our results indicate that patients with a combined overdose of dihydropyridines and ACEIs/ARBs had significantly lower median nadirs of SBP and MAP; and a significantly higher proportion experienced hypotension, bradycardia, received intravenous fluids treatment and vasopressors and/or antidotes. The rate of receiving intravenous fluids was also higher in the mixed ingestion group. A target MAP of at least 65 mmHg is recommended for sufficient organ perfusion [27], and a larger proportion of patients in the mixed ingestion group did not meet this target on admission. These associations were minimally changed after adjustment for other factors associated with these outcomes (dose and age).

Overdoses of ARBs/ACEIs are mostly benign and rarely cause serious adverse effects requiring vasopressors [15,17]. Though there have been a few cases of hypotension that were responsive to fluid and vasopressor therapy [28,29], most case reports of ARB/ACEI overdose do not report significant hypotension [16,29–31]. There was a single case of
hypotension in a case series of 19 paediatric overdoses of ARBs or ACEIs and the patient required no treatment [14]. In a case series of 206 ARB overdoses, only one paediatric patient required treatment with intravenous fluids [17]. In another case series of 33 ACEI overdoses, only one patient required vasopressors, but it was unclear whether they belonged to the 13 cases who had concurrent ingestions with other antihypertensives [32]. Furthermore, ARBs/ACEIs were not the primary cause of any deaths in the 2017 Annual Report of the American Association of Poison Control Centres [4]. Despite this exceptionally low toxicity, our results show that severity appears to be significantly worse when an ARB/ACEI is added to a dihydropyridine in overdose. This potential synergism can be explained mechanistically. Theoretically, a dihydropyridine overdose will cause widespread peripheral vasodilation, triggering homeostatic counter-regulatory mechanisms through the activation of the renin-angiotensin-aldosterone system (RAAS; Figure 5). However, the RAAS homeostatic response is inhibited with concurrent overdose of ARB/ACEI [33]. Furthermore, this combination may also reduce sympathetic outflow [34]. With these mechanisms compromised, dihydropyridines and ARBs/ACEIs are predicted to act synergistically, blunting the homeostatic vasoconstrictive response to endogenous and exogenous catecholamines [8,9,21]. Indeed, mixed ingestion patients in our study required more haemodynamic support as well as less conventional therapies such as methylene blue and high-dose insulin euglycaemic therapy (HIET), likely due to developing a more catecholamine-resistant shock [35]. Furthermore, while a typical dihydropyridine overdose presents with hypotension and reflex tachycardia [7], inhibition of catecholamine release with AT1 blockade may explain the clinically higher rate of bradycardia and lower median lowest HR in the mixed ingestion group.

In addition, amlodipine and various ARBs and ACEIs have been shown to increase nitric oxide (NO) mediated vasodilation, which may contribute to the prolonged, refractory hypotension experienced with combination overdoses. Amlodipine strongly inhibits ACE to a similar extent to the ACEI enalapril at equal concentrations in vitro [36], causing an increase in bradykinin and potential activation of bradykinin 2 receptors to produce vasodilatory NO from endothelial cells in animal models [36–38]. Zhang et al. [39] determined that of the two enantiomers of amlodipine, the R+ enantiomer was responsible for NO production independent of calcium channel blockade, whilst the S-enantiomer caused calcium channel antagonism only. It is noted that NO production is not demonstrated in nifedipine [36], and there is a lack of evidence regarding this mechanism in lercanidipine or felodipine. Furthermore, the ARB olmesartan was also shown to increase NO release at an amount dependent on the type of endothelial nitric oxide synthase (eNOS) variant [40]. Imanishi et al. [41] also demonstrated in a rabbit model that acetylcholine-induced NO release was significantly higher in groups treated with the ACEI enalapril and/or the ARB losartan, when compared with controls. This is the first large case series of dihydropyridine overdoses with or without an ARB/ACEI that provided statistical analysis. There are only nine case reports available in the literature detailing mixed overdoses with dihydropyridine CCBs and ARBs/ACEIs [8,9,18–24]. Of these, all cases developed profound hypotension and received intravenous fluids. While there could be publication bias reporting severe cases, this observation is in keeping with our results. The lowest MAP during admission within these case reports ranged from 39 mmHg [23] to 54 mmHg [9], well below targets for adequate tissue perfusion. Most cases were refractory to conventional therapies, requiring extra corporeal membrane oxygenation [20,23], methylene blue [19,23], continuous venovenous haemofiltration [8,18], intravenous lipid emulsion [8,20,21] and molecular adsorbent recirculating system [8] to facilitate recovery from toxicity. Our results also reflect the

Figure 5. Synergistic Actions of ARB/ACEI and CCBs. Red indicates elements contributing to decreased BP and green indicates elements contributing to increased BP. CCBs cause vasodilation, thereby decreasing peripheral resistance and blood pressure. The green dotted line represents the subsequent activation of the RAAS by increased renin release to raise peripheral resistance. ACEIs and ARBs antagonise steps within the RAAS, disrupting homeostatic responses and causing a synergistic decrease in peripheral resistance and blood pressure.
need for more aggressive therapies for patients with a mixed ingestion, where HIET and methylene blue were used within the mixed ingestion group but not in the single ingestion group.

With increasing rates of hypertension and cardiovascular disease, there will be an inevitable increase in the prescription and overdose of combination therapies of dihydropyridine CCBs and ARBs/ACEIs. Given the worsened haemodynamic and treatment requirement with a mixed ingestion overdose found in this study, physicians should be cautious in prescribing these combination products in patients with a history of deliberate self-poisoning.

**Limitations**

In this study, our recruitment through poison centre calls may have been biased towards more severe cases. The dose information may also not be accurately recorded [42], and this may therefore affect the dose–outcome relationship in our results. Drug levels were not available to confirm or quantify dihydropyridine ingestions as they were not routinely performed. However, other Australian data have reported a high correlation between plasma levels and patient-reported doses [43]. Furthermore, eighty cases (72 from PIC, 8 from toxicology units) could not be included in the study as their medical records could not be retrieved by the authors. This reflects the greater difficulties in using Poison Centre databases for patient recruitment as medical records must then be requested from individual hospitals nationwide.

Our study was not sufficiently large enough to explore the differences between individual drugs within the dihydropyridines class. This study was conducted under the assumption that all dihydropyridines have the same mechanism of action. However, the literature suggests that amlodipine, but not nifedipine, enhances NO release from endothelial cells [36]. Furthermore, NO-dependent dilatory mechanisms have not been well-studied in felodipine and lercanidipine. This raises the possibility that each drug within the dihydropyridine class could act with unique mechanisms that may or may not be increased by the coingestion of ARBs/ACEIs in overdose. Although most of our patients ingested amlodipine (84% in the mixed group and 59% in the single ingestion group), the mixed ingestion group had a significantly higher proportion of amlodipine ingestions which could have contributed to the observed differences between each group. Further mechanistic information and larger clinical studies would be needed to explore whether such differences are important in overdose.

**Conclusions**

Mixed overdose of dihydropyridine CCBs with an ARB/ACEI were associated with more hypotension, bradycardia and a significantly lower median lowest SBP/MAP than single overdose and required more haemodynamic support. Hypotension is more common in patients following a mixed overdose of dihydropyridines with ARBs/ACEIs, increased dosage of dihydropyridines and decreased age. These results could be attributed to synergistic interaction between dihydropyridine CCBs and ARB/ACEI in overdoses.

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**Disclosure statement**

No potential conflict of interest was reported by the author(s).

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