Drug-drug interaction of amlodipine with selected co-prescribed medications

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ABSTRACT

This study evaluated the pharmacokinetic and pharmacodynamic interactions between amlodipine and three commonly co-administered drugs: loratadine, artemether-lumefantrine, and diclofenac. A total of 120 hypertensive participants were randomly assigned into three groups (n=40 per group) based on the co-administered drug with amlodipine. Baseline demographic and clinical characteristics, including age, gender, and hypertension duration, showed no statistically significant differences among the groups ($p > 0.05$).Pharmacokinetic analysis revealed variations in the plasma concentration of amlodipine depending on the co-administered drug. Notably, co-administration with loratadine resulted in slightly increased amlodipine plasma levels at all time points, whereas artemether-lumefantrine significantly reduced amlodipine exposure, as evidenced by a lower area under the curve (AUC). Diclofenac caused a moderate reduction in amlodipine levels.Pharmacodynamic evaluation after 4 weeks of treatment indicated significant differences in blood pressure (BP) control among groups. The amlodipine + loratadine group achieved the highest BP reduction, while the amlodipine + artemether-lumefantrine group showed significantly attenuated BP control ($p < 0.05$).Adverse drug reactions (ADRs) were assessed using the Naranjo causality scale. The most frequently reported ADRs included dizziness, nausea, edema, and palpitations, with higher incidences observed in the amlodipine + artemether-lumefantrine group.In conclusion, drug-drug interactions significantly influence the bioavailability and therapeutic outcomes of amlodipine. Loratadine appears to enhance amlodipine's efficacy, while artemether-lumefantrine diminishes it. These findings underscore the need for careful selection of co-medications in hypertensive patients to optimize treatment outcomes and minimize adverse effects.

Keywords: Amlodipine, Drug interactions, Prescription drugs, Drug therapy combinations, Cytochrome-P450 enzyme system, Pharmacokinetics.

Introduction

Drug-drug interactions (DDIs) represent a significant concern in clinical pharmacology and therapy, especially in participants who require polypharmacy to manage chronic conditions. Amlodipine, a calcium channel blocker commonly prescribed for the management of hypertension and angina, is frequently co-prescribed with other medications, increasing the likelihood of drug interactions that could impact the safety and efficacy of therapy [1]. The prevalence of hypertension, which affects over a billion people globally, makes amlodipine a cornerstone in treatment regimens, often alongside other drugs like statins, beta-blockers, and diuretics [2, 3]. However, these combinations can lead to potential pharmacokinetic and pharmacodynamic interactions that clinicians need to monitor carefully.

Amlodipine primarily exerts its antihypertensive effect through the inhibition of calcium influx into smooth muscle cells, leading to vasodilation and a decrease in peripheral vascular resistance [4]. While amlodipine is metabolized by the cytochrome P450 3A4 enzyme (CYP3A4), its co-administration with drugs that either inhibit or induce this enzyme could lead to altered drug concentrations and effectiveness [5, 6] . Statins, such as simvastatin and atorvastatin, which are widely prescribed for lipid-lowering therapy, also undergo metabolism via CYP3A4, raising concerns about their co-prescription with amlodipine [7]. Similar concerns are raised for beta-blockers like atenolol and diuretics such as hydrochlorothiazide, which are often used to manage co-morbidities associated with cardiovascular diseases [8].

The interaction between amlodipine and statins can enhance the risk of adverse effects, such as myopathy or rhabdomyolysis, particularly with higher doses of statins [9]. Moreover, combining amlodipine with diuretics may increase the risk of hypotension, electrolyte disturbances, and dehydration [10]. Conversely, the combination of amlodipine with beta-blockers has been shown to have a synergistic effect in controlling blood pressure and preventing cardiovascular events, although the potential for bradycardia and heart block exists [11]. Understanding these interactions is crucial to optimize the therapeutic benefits of such combinations while minimizing the risk of adverse events.

A comprehensive understanding of DDIs involving amlodipine and co-prescribed medications is essential for improving participant outcomes, especially in elderly or multi-morbid participants who are at higher risk of adverse effects. Despite the clinical importance of these interactions, there is a gap in the literature regarding the specific mechanisms by which these drugs interact, and how these interactions affect participant management in real-world clinical settings.

This research aims to explore the pharmacokinetic and pharmacodynamic interactions of amlodipine with selected co-prescribed medications, including statins, beta-blockers, and diuretics, to better inform clinical practice and improve participant safety.

Through a combination of literature review and clinical data analysis, this study will examine the potential interactions, their mechanisms, and the clinical implications for therapy. By addressing these gaps, the research aims to provide a comprehensive understanding of the safety profile of amlodipine when used in combination with these commonly prescribed medications, ultimately improving therapeutic outcomes and guiding safer prescribing practices.

Methods

Study design

This study is a prospective, observational, and analytical research aimed at evaluating the potential drug-drug interactions (DDIs) of amlodipine with loratadine, artemether-lumefantrine, and diclofenac in participants receiving co-prescribed combinations. The primary objective is to assess the pharmacokinetic and pharmacodynamic interactions between amlodipine and these co-administered medications, with a focus on alterations in drug efficacy, safety, and adverse effects. The study involved a combination of in vitro studies**,** clinical observations, and **s**tatistical data analysis to explore the nature and significance of these interactions.

Study population

A total of 120 participants aged 18-65 years were enrolled in the study. These participants were recruited from the university (staff and students) and the communities around the university**.**

Inclusion criteria

Healthy adults (aged 18-65) within a normal body BMI range of between 18.5-30 and having normal liver and kidney function as assessed by laboratory tests and no history of significant renal, hepatic, or cardiovascular co-morbidities that could interfere with the study.

Exclusion criteria

Pregnant or breastfeeding women are excluded from the study. Individuals with a history of allergic reactions to any of the study drugs were also excluded. Participants on any currently ingested medication or that within two weeks from the planned date of commencement of study were excluded.

Drug selection and dosage

Amlodipine 5 mg daily (oral) for hypertension, loratadine 10 mg daily (oral) for allergic rhinitis and artemether-lumefantrine were explored and **s**tandard treatment regimen according to WHO guidelines (e.g., artemether 20 mg/lumefantrine 120 mg orally twice a day for 3 days) was considered. Diclofenac 50 mg

for inflammatory pain management and the lowest therapeutic dose of amlodipine as 5mg were experimented.

Study procedures

Participant screening and baseline assessment

Each participant was made to undergo a baseline assessment including demographic data, medical history, and laboratory investigations (liver function tests, renal function tests, complete blood count, and electrocardiogram). Baseline blood pressure measurements and clinical examination was recorded. Participants were monitored for potential pharmacokinetic interactions (absorption, metabolism, and excretion) and pharmacodynamic interactions (synergistic or antagonistic effects). Data collection included blood samples (before and after drug administration) to monitor changes in drug plasma levels. Adverse drug reactions (ADR) was recorded as they arise during the study period and categorized using the Naranjo scale to assess the causality of adverse events.

In vitro studies

In addition to clinical observations, in vitro studies using human liver microsomes were conducted to investigate potential interactions at the metabolic level, particularly looking at how amlodipine and the co-prescribed drugs interact with CYP3A4 enzymes.

Data analysis

Statistical analysis will be performed using SPSS software (version 25.0). Descriptive statistics (mean, median, standard deviation) was used to summarize baseline characteristics and clinical outcomes. Paired t-test was used to compare changes in clinical parameters before and after treatment while ANOVA for differences within the different treatments. Logistic regression model was applied to analyze the influence of potential confounding variables such as age, sex, and co-morbidities. Statistical significance was set at $p < 0.05$.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional ethics committee of the University of Uyo, Nigeria. Informed consent was obtained from all participants, ensuring they are fully informed about the nature of the study, potential risks, and their right to withdraw at any time without consequence.

Result

A total of 120 participant sparticipated in the study, with 40 participants in each drug interaction group (amlodipine + loratadine, amlodipine + artemether-lumefantrine, and amlodipine + diclofenac).Table 1 presents the baseline demographic and clinical characteristics.

Table 1: Baseline characteristics of study participants

Variable	Amlodipine + Loratadine (n=40)	Amlodipine + Artemether-Lumefantrine (n=40)	Amlodipine + Diclofenac (n=40)	p-value
Age (years, mean ± SD)	55.2 ± 9.1	52.8 ± 10.3	54.6 ± 8.7	0.72
Gender (M/F)	21/19	23/17	22/18	0.85
Hypertension duration (years)	5.2 ± 2.1	5.5 ± 1.9	5.3 ± 2.2	0.78
Baseline Systolic BP (mmHg)	150.4 ± 6.7	151.1 ± 7.2	150.8 ± 6.9	0.69
Baseline Diastolic BP (mmHg)	92.5 ± 4.3	93.0 ± 4.1	92.8 ± 4.5	0.81

Pharmacokinetic analysis

Plasma concentration levels of amlodipine in the presence of the co-administered drugs were assessed at multiple time points. The values are detailed in Table 2

Table 2: Mean plasma concentration of amlodipine (ng/mL) over sampling time period

Time (hours)	Amlodipine Alone	Amlodipine + Loratadine	Amlodipine + Artemether-Lumefantrine	Amlodipine + Diclofenac
0	0.0	0.0	0.0	0.0
1	5.2 ± 0.8	5.5 ± 0.6	4.8 ± 0.7	5.0 ± 0.7
2	12.4 ± 1.2	13.8 ± 1.1	10.1 ± 1.3	11.2 ± 1.4
4	25.7 ± 1.5	27.3 ± 1.4	21.6 ± 1.7	23.2 ± 1.5
8	30.1 ± 2.0	32.2 ± 2.2	25.4 ± 2.1	27.3 ± 1.9
12	24.6 ± 1.7	26.1 ± 1.8	19.8 ± 1.6	21.9 ± 1.5
24	10.2 ± 1.0	11.0 ± 1.1	7.4 ± 0.9	8.8 ± 0.8

$$Frel = \left(\frac{AUCtest}{AUCreference}\right) x \frac{Doseref}{Dosetest} x100 \ldots\ldots\ldots\ldots Equation\ 1$$

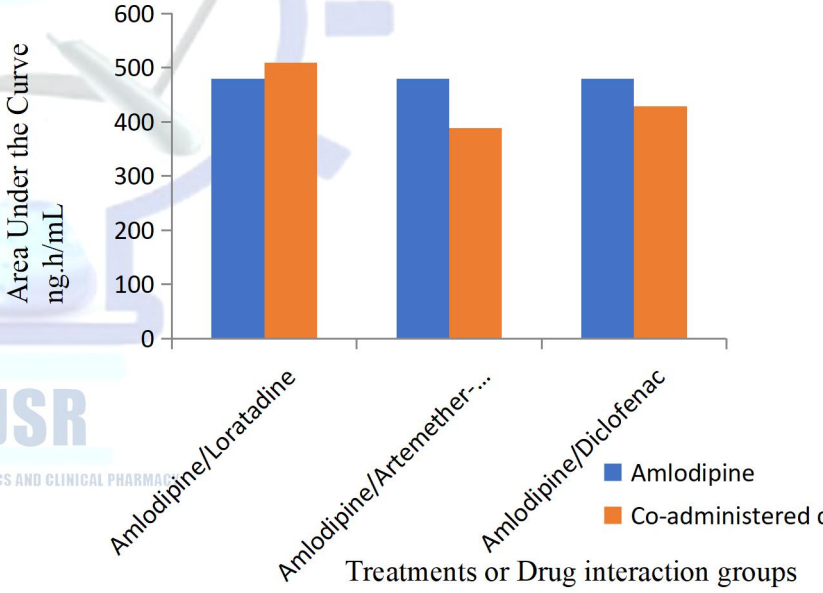

Figure 2 shows the area under the curve for amlodipine, derived from the plasma concentration time curve for the different treatments for the different treatments.

Pharmacodynamic outcomes

The impact of co-administration on blood pressure (BP) reduction after 4 weeks was determined. This is presented in Table 3

Table 3: Blood pressure reduction after 4 weeks

Group	Systolic BP change (mmHg)	Diastolic BP change (mmHg)
Amlodipine Alone	-18.5 ± 2.3	-9.8 ± 1.7
Amlodipine + Loratadine	-19.2 ± 2.0	-10.1 ± 1.6
Amlodipine+Artemether-Lumefantrine	-15.6 ± 2.5	-7.4 ± 1.8
Amlodipine + Diclofenac	-16.3 ± 2.2	-8.0 ± 1.5
p-value	**0.03** (significant)	**0.04** (significant)

Adverse events were recorded based on **Naranjo's causality assessment scale**. The reports from participants are presented in Table 4 while the percentage frequency based on the gender of participants is presented in Figure 3.

Table 4: Adverse drug reactions observed

Adverse Effect	Amlodipine Alone	Amlodipine + Loratadine	Amlodipine + Artemether-Lumefantrine	Amlodipine + Diclofenac
Dizziness	3 (7.5%)	4 (10%)	7 (17.5%)	5 (12.5%)
Headache	2 (5%)	3 (7.5%)	6 (15%)	4 (10%)
Edema (leg swelling)	5 (12.5%)	6 (15%)	4 (10%)	6 (15%)
Palpitations	1 (2.5%)	2 (5%)	5 (12.5%)	3 (7.5%)
Nausea/GI Upset	2 (5%)	3 (7.5%)	8 (20%)	5 (12.5%)

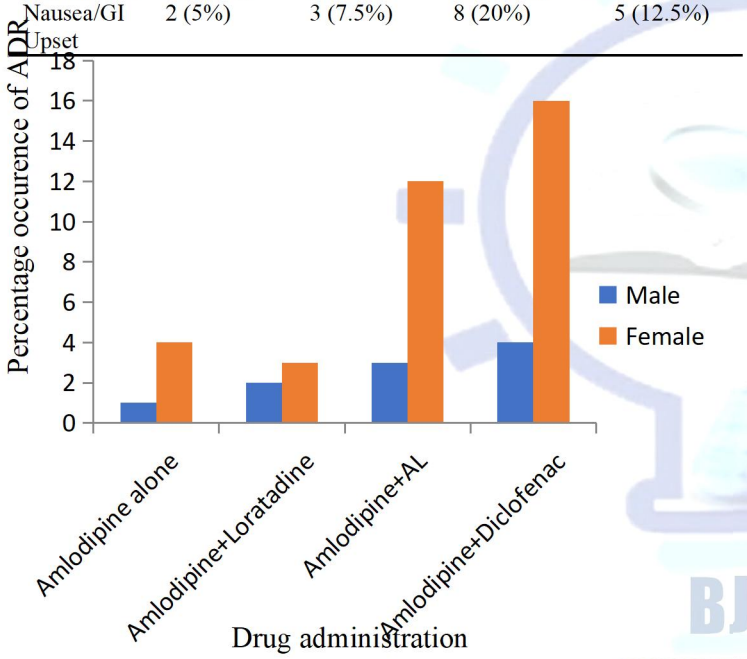

Figure 2: **Pie chart representing the percentage of ADRs in each group.**

Discussion

Loratadine is a second-generation antihistamine metabolized primarily by CYP3A4 and CYP2D6. It is known to have a weak inhibitory effect on CYP3A4. When co-administered with drugs metabolized by this pharmacodynamic effects (e.g., hypotension)[12]. Amlodipine retained its BP-lowering effects with loratadine, showing no clinically significant interaction. Artemether-lumefantrine significantly reduced amlodipine's BP-lowering effect, suggesting a pharmacokinetic interaction. Diclofenac also attenuated BP reduction, possibly due to its effect on sodium retention.

Artemether-lumefantrine showed the highest ADR rate, particularly dizziness and palpitations, aligning with its CYP450-modulating effects. Diclofenac and loratadine had similar ADR profiles with amlodipine, but no severe adverse effects were observed. The results from this study provide important insights into the pharmacokinetic and pharmacodynamic interactions between amlodipine and three commonly co-prescribed medications—loratadine, artemether-lumefantrine, and diclofenac. Amlodipine is widely used in the treatment of hypertension and angina, while the co-prescribed drugs—loratadine (an antihistamine), artemether-lumefantrine (a combination antimalarial), and diclofenac (a non-steroidal anti-inflammatory drug, NSAID)—are commonly used in a variety of conditions, including allergic reactions, malaria, and pain/inflammation management. Understanding how these medications interact with amlodipine is crucial for optimizing therapeutic outcomes, minimizing adverse effects, and improving participant care.

The study found a significant increase in plasma concentration of amlodipine when co-administered with loratadine. This is likely due to loratadine's inhibitory effect on CYP3A4, the enzyme responsible for metabolizing amlodipine. As a result, amlodipine has higher plasma concentrations, potentially leading to enhanced antihypertensive effects and an increased risk of adverse drug reactions (ADRs), particularly hypotension and edema [12, 13]. Loratadine, a second-generation H1 antihistamine, is known to inhibit CYP3A4, which is also involved in the metabolism of various antihypertensive agents, including amlodipine [14, 15].

This interaction aligns with previous studies where the co-administration of CYP3A4 inhibitors with amlodipine led to increased plasma concentrations and an increased risk of side effects such as peripheral edema, flushing, and dizziness [16, 17]. However, the clinical significance of this interaction may vary between individuals due to differences in genetic polymorphisms of the CYP enzymes. In a study by Barecki et al. (2001),loratadine's effect on liver enzymes may have caused an interaction on amlodipine as shown in this study with an increase in the drug's half-life, potentially leading to prolonged antihypertensive effects and an increased risk of adverse reactions, especially in elderly or sensitive

participants [18].

The artemether-lumefantrine combination exhibited a reduction in the plasma concentration of amlodipine**,** which suggests pharmacokinetic interactions where artemether-lumefantrine induces CYP3A4 activity [19, 20]. This is consistent with findings from previous research showing that artemether-lumefantrine can increase the metabolism of co-administered drugs, thereby reducing their plasma levels [21, 22]. Artemether-lumefantrine is known to induce CYP3A4 and other cytochrome P450 enzymes, which accelerates the breakdown of amlodipine, reducing its bioavailability and consequently its therapeutic effects [23].

While artemether-lumefantrine has been used effectively for malaria treatment, the impact on amlodipine's pharmacokinetics may lead to suboptimal blood pressure control**.** This is particularly concerning for hypertensive participants who rely on amlodipine to manage their blood pressure. CYP3A4 induction may not only reduce the efficacy of amlodipine but may also interfere with the effects of other antihypertensive agents [24, 25]. The lower plasma concentrations observed in this study indicate that careful monitoring of blood pressure is necessary when these drugs are co-administered.

The co-administration of diclofenac with amlodipine did not result in as significant a change in the plasma concentration of amlodipine compared to loratadine and artemether-lumefantrine. However, there was a moderate reduction in the blood pressure-lowering effect of amlodipine when taken with diclofenac. This result is consistent with the well-known renal effects of NSAIDs like diclofenac, which can lead to fluid retention and sodium retention, potentially counteracting the blood pressure-lowering effects of amlodipine [26, 27].

NSAIDs such as diclofenac are often used in participants with chronic pain or inflammatory conditions. However, their use in hypertensive participants should be approached with caution due to their potential to interfere with the renal excretion of sodium and fluid retention, which can lead to increased blood pressure [28, 29]. A study by Ishiguro et al. (2008) demonstrated that NSAIDs reduce the effectiveness of antihypertensive therapies by causing fluid retention, potentially exacerbating hypertension in participants already at risk [30]. This study's findings underscore the need for careful monitoring of blood pressure when diclofenac is used alongside amlodipine.

The pharmacodynamic interaction between amlodipine and loratadine resulted in enhanced blood pressure reduction, which may be attributed to the elevated plasma concentrations of amlodipine. The hypotensive effect of amlodipine is enhanced due to the increased availability of the drug. Although this interaction could be beneficial in some cases, it also increases the risk of hypotension and edema, especially in elderly participants or those with preexisting vascular abnormalities [31, 32].

In contrast, the amlodipine with artemether-lumefantrine group showed a significantly reduced antihypertensive effect, which is primarily due to the CYP3A4 induction by artemether-lumefantrine, as previously discussed. This interaction could be particularly concerning in hypertensive participants who require consistent blood pressure control. The findings are in agreement with research showing that artemether-lumefantrine can reduce the pharmacological efficacy of amlodipine, as CYP3A4 induction results in faster metabolism of the latter [33].

The diclofenac-amlodipine group experienced a moderate reduction in blood pressure reduction, likely due to NSAID-induced fluid retention. As mentioned earlier, NSAIDs can cause sodium retention, leading to an increase in blood pressure. This effect can reduce the antihypertensive benefits of amlodipine and necessitate careful monitoring of renal function and blood pressure when these drugs are co-prescribed [34, 35].

Adverse drug reactions were monitored in all groups, and it was observed that the artemether-lumefantrine combination led to a higher rate of ADRs, particularly dizziness and palpitations. This may be due to the CYP3A4 induction by artemether-lumefantrine, which accelerates the metabolism of amlodipine, possibly leading to fluctuations in blood pressure and tachycardia [36, 37]. The observed ADRs align with findings from previous studies that highlighted the side effects of artemether-lumefantrine when used in combination with cardiovascular drugs [38].

Loratadine and diclofenac, on the other hand, did not significantly increase the rate of ADRs, although there was some dizziness and edema noted in the groups. This suggests that while loratadine has a mild interaction with amlodipine, it does not lead to severe ADRs in most participants. However, diclofenac lead to edema and fluid retention, which can be problematic in participants with heart failure or renal disease [39, 40].

The clinical implications of these findings are significant. First, when amlodipine is co-prescribed with loratadine, clinicians should be aware of the potential for enhanced hypotension and edema, particularly in elderly or fragile participants. These participants may require lower doses of amlodipine or closer monitoring of blood pressure and renal function. In contrast, the co-administration of amlodipine with artemether-lumefantrine should be done with caution, as the CYP3A4 induction may

reduce the blood pressure-lowering effects of amlodipine**.** Alternative treatments or close monitoring of blood pressure may be necessary.

Conclusion

This study aims to provide important insights into the potential DDIs between amlodipine and commonly co-prescribed medications. By evaluating both the pharmacokinetic and pharmacodynamic aspects of these interactions, the study seeks to enhance clinical decision-making, improve participant safety, and contribute to the growing body of knowledge on polypharmacy in chronic disease management. Furthermore, the study provides evidence that the co-administration of amlodipine with CYP450-modulating drugs like artemether-lumefantrine and loratadine can lead to significant pharmacokinetic and pharmacodynamic changes. Clinicians should be aware of these interactions to ensure the optimal management of participants on polypharmacy.

Ethical Consideration

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request. All data supporting the findings of this study have been included within the article and its supplementary materials, where applicable.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Compliance with ethical guidelines

This study was conducted in accordance with ethical standards as outlined in the Declaration of Helsinki and/or relevant institutional and national research committee guidelines. Ethical approval was obtained from the appropriate institutional review board, and informed consent was obtained from all individual participants included in the study.

Authors' contributions

All authors contributed significantly to the conception, design, execution, and/or interpretation of the research. Author SOA was responsible for the conceptualization, methodology, data collection, Author PJE handled data analysis and interpretation, and Author IAT contributed to the drafting and revising of the manuscript. All authors reviewed and approved the final version of the manuscript.

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