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CLINICAL PHARMACOLOGY OF AMLODIPINE

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ABSTRACT

Amlodipine, a dihydropyridine, is a multiple Ca^{2+} channel blocker approved for clinical use. An increased concentration of cytosolic Ca^{2+} causes increased concentration in both cardiac and vascular smooth muscle cells. In cardiac myocytes, the entry of extracellular Ca^{2+} causes a larger release from intracellular stores (Ca^{2+}-induced Ca^{2+} release) and thereby initiates the concentration twitch. In smooth muscle cells, the entry of Ca^{2+} plays a dominant role, but the release of Ca^{2+} from the intracellular storage sites also contributes to contraction of vascular smooth muscle, particularly in some vascular beds. The efficacy and safely of amlodipine, the prophylaxis with amlodipine, the treatment of hypertensive patients with amlodipine, and the trials conducted with amlodipine have been reviewed. Amlodipine is metabolized by CYP3A4 and CYP3A5. The pharmacokinetics of amlodipine have been studied in healthy volunteers following single and repeated administrations and following repeated administration the elimination half-life of amlodipine is about 45 hours. The elimination half-life of amlodipine is longer than the interval between amlodipine administrations thus the plasma concentration of amlodipine increases with repeated administrations. The interaction of amlodipine with drugs and the toxicity induced by amlodipine have been reviewed. The aim of this study is to review the efficacy and safely of amlodipine, the prophylaxis with amlodipine, the treatment of hypertensive patients with amlodipine, and the trials conducted with amlodipine. In addition, the metabolism of amlodipine, the pharmacokinetics of amlodipine, the interaction of amlodipine with drugs, and the toxicity induced by amlodipine have been reviewed.

KEYWORDS: Amlodipine, drug-interactions, efficacy-safely, metabolism, pharmacokinetics, prophylaxis, toxicity, treatment, and trials.

INTRODUCTION

Mechanisms of action of amlodipine

Amlodipine, a dihydropyridine, is a multiple Ca^{2+} channel blocker approved for clinical use. An increased concentration of cytosolic Ca^{2+} causes increased concentration in both cardiac and vascular smooth muscle cells. In cardiac myocytes, the entry of extracellular Ca^{2+} causes a larger Ca^{2+} release from intracellular stores (Ca^{2+}-induced Ca^{2+}release) and thereby initiates the contraction twitch. In smooth muscle cells, entry of Ca^{2+} plays a dominant role, but the release of Ca^{2+} from the intracellular storage sites also contributes to contraction of vascular smooth muscle, particularly in some vascular beds. Cytosolic Ca^{2+} concentrations can be increased by diverse contractile stimuli in vascular smooth cells. Many hormones and autacoids increase Ca^{2+} influx through so-called receptor-operated channels, whereas increases in external concentration of K^+ and depolarizing electrical stimuli increase Ca^{2+} influx through voltage-gated or "potential operated" channels. Amlodipine produces its effects by binding to the α_1 subunit of the L-type voltage-gated Ca^{2+} channels and lowering Ca^{2+} flux through the channel.[1]

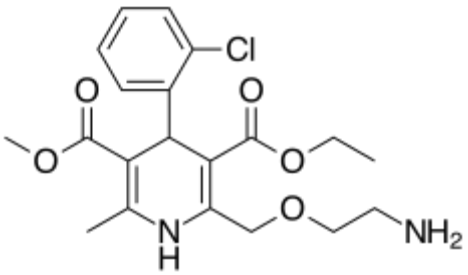
Pharmacological actions of amlodipine

Depolarization of vascular smooth muscle cells depends primarily on the influx of Ca^{2+}. At least three distinct mechanisms may be responsible for contraction of vascular smooth cells. First, voltage-gated Ca^{2+} channels open in response to depolarisation of the membrane, and extracellular Ca^{2+} moves down its electrochemical gradient into the cell. After closure of Ca^{2+} channels, a finite period of time is required before the channels open again in response to a stimulus. Second, agonist-induced contractions that occur with-out depolarization of the membrane result from stimulation of the G_q-phospholipase C (inositol 1,4,5-triphosphate) pathway, resulting in the release of intracellular Ca^{2+} from the sarcoplasmic reticulum. Emptying of intracellular Ca^{2+} stores may trigger further influx of extracellular Ca^{2+} (store-operated Ca^{2+} entry), but its relevance in smooth muscle is unresolved. Third, receptor-operated Ca^{2+} channels allow the entry of extracellular Ca^{2+} in response to receptor occupancy. An increase in cytosolic Ca^{2+}

results in enhanced binding of Ca^{2+} to calmodulin. The Ca^{2+}-calmodulin complex in turn activates myosin light-chain kinase, with resulting phosphorylation of the myosin light chain. Such phosphorylation promotes interaction between actin and myosin and leads to sustained contraction of smooth muscle. Ca^{2+} channel blockers inhibit the voltage-dependent Ca^{2+} channels in vascular smooth muscle and decreases Ca^{2+} entry. Amlodipine relaxes arterial smooth muscle and thereby decrease arterial resistance, blood pressure, and cardiac afterload.[1]

Absorption, distribution, metabolism, and elimination of amlodipine

Amlodipine has low absorption and a prolonged effect. With an elimination half-life of about 35 hours, plasma levels and effect increase over 7 to 19 days of daily administration of a constant dose, resulting in a concentration with modest peaks and troughs. Such a profile allows the body to adapt and is associated with less reflex tachycardia. The bioavailability of amlodipine is reduced, in some cases markedly, by first-pass metabolism by CYP3A4 enzymes in the interstitial epithelium and the liver. This has two consequences: (1) the bioavailability of amlodipine may be increased by intake of inhibitors of CYP3A4, such as macrolide and imidazole antibiotics, antiretroviral agents and grapefruit juice. The bioavailability is reduced by inducers of CYP3A4, such as rifampin and carbamazepine. (2) Some Ca^{2+} channel blockers (particularly verapamil) are strong CYP3A4 inhibitors and cause clinically relevant drug interactions with other CYP3A4 inhibitors, such as simvastatin and atorvastatin.[1]



Amlodipine chemical structure (molecular weight = 408.88 grams/mole)

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "amlodipine efficacy, safety", "amlodipine prophylaxis", "amlodipine treatment", "amlodipine trials", "amlodipine metabolism", "amlodipine pharmacokinetics", "amlodipine drug interactions", and "amlodipine toxicity". In addition the book: Goodman@Gilman's. The Pharmacological basis of Therapeutics[1] has been consulted.

RESULTS

Efficacy and safely of amlodipine

Seven studies have been reported on the efficacy and safely of amlodipine. Patients with an average sitting diastolic blood pressure ≥ 95 and ≤ 115 mmHg received 5 mg of amlodipine once daily and the dose was adjusted to 10 mg once daily after 4 weeks of treatment to achieve a target sitting diastolic blood pressure ≤ 90 mmHg. This treatment produced significant (P-value < 0.05) falls in the systolic and diastolic blood pressures by 23.7 and 17.3 mmHg, respectively, with no effect on heart rate. Amlodipine effectively lowered the systolic and diastolic blood pressures in hypertensive patients and was found to be safe and well-tolerated.[2] Amlodipine was administered once daily at the dose of 5 mg for 8 weeks. If the blood pressure was ≥ 140/90 mmHg or the sitting diastolic blood pressure was not decreased by ≤ 10 mmHg from that at baseline after 4 weeks of treatment the dose of amlodipine was increased to 10 mg. The blood pressure was measured twice daily every 4 weeks and the mean value was recorded. The mean diastolic blood pressure was 97.4±5.8 mmHg before treatment and it was lowered to 84.1±8.8 mmHg at the end of treatment. Once daily amlodipine effectively lowered diastolic blood pressure in hypertensive patients and was found to be safe and well-tolerated.[3] Amlodipine was administered at the daily dose of 5 mg for 6 months to 4,277 hypertensive patients. By the end of treatment, 1,617 patients (37.8%) achieved the therapeutic goal (systolic and diastolic blood pressures of 140 and < 90 mmHg, respectively) and there were only 20 serious adverse-effects and none was related to amlodipine. Amlodipine achieved therapeutic systolic and diastolic blood pressures in a higher proportion in hypertensive patients and was found to be safe and well-tolerated.[4] Nifedipine was administered at the daily dose of 30 mg for 8 weeks to 102 hypertensive patients and amlodipine was administered at the daily dose of 5 mg for 8 weeks to 105 hypertensive patients. Before treatment, the mean systolic and diastolic blood pressures were 161 and 102 mmHg, respectively, in patients who received nifedipine and they were 160 and 102 mmHg, respectively, in patients who received amlodipine patients. At the end of treatment, the mean systolic and diastolic blood pressures were 141 and 85 mmHg, respectively, in patients who received nifedipine and they were 141 and 86 mmHg, respectively, in patients who received amlodipine. The adverse-effects occurred in 9 patients (8.8%) who received nifedipine and in 6 patients (5.7%) who received amlodipine. Nifedipine and amlodipine were found to be similarly efficacious in lowering the systolic and diastolic blood pressures in hypertensive patients and were found to be safe and well-tolerated.[5] Amlodipine was administered once daily at the dose of 5 mg and valsartan was co-administered once daily at the dose of 160 mg to 159 hypertensive patients. The mean systolic and diastolic blood pressures were decreased by 17.97 and by 8.58 mmHg, respectively. Amlodipine and valsartan combination effectively lowered the systolic and diastolic blood pressures in hypertensive patients and

was found to be safe and well-tolerated.[6] It was compared the efficacy and safely of manidipine to those of amlodipine in treatment of hypertensive patients. Manidipine was administered at the daily dose of 20 mg to 421 hypertensive patients and amlodipine was administered at the daily dose of 10 mg to 452 hypertensive patients and both drugs were administered for 12 weeks. The mean systolic blood pressure was reduced by 18.3 mmHg after manidipine administration and by 17.3 mmHg after amlodipine administration. The mean diastolic blood pressure was reduced by 8.5 mmHg after manidipine administration and by 10.5 mmHg after the amlodipine administration. The adverse-effects were lower (P-value = 0.001) in patients who received manidipine than in those who received amlodipine. Manidipine was effective as amlodipine in lowering the systolic and diastolic blood pressures in hypertensive patients and was better tolerated.[7] Amlodipine was administered at the daily dose of 2.5 mg to 5 mg for 8 weeks to 35 hypertensive patients with renal dysfunction. The target reduction in systolic and diastolic blood pressures was achieved in 28 of 35 patients (80.0%), it was decreased in 4 patients (11.4%), and it was unchanged in only 3 patients (8.6%). This treatment effectively lowered the systolic and diastolic blood pressures, was found to be safe and well-tolerated, and amlodipine did not accumulate in hypertensive patients with renal dysfunction.[8] These results indicate that amlodipine, administered at the daily dose of 5 to 10 mg, lowers the systolic and diastolic blood pressures in hypertensive patients and this treatment is well-tolerated. Nifedipine is efficacious as amlodipine in lowering the systolic and diastolic blood pressures in hypertensive patients and both drugs are well-tolerated. The combination of amlodipine with valsartan lowers the blood pressure in hypertensive patients and this drug combination is well-tolerated. Manidipine is effective as amlodipine in lowering the systolic and diastolic blood pressures in hypertensive patients but manidipine is better tolerated than amlodipine.

Prophylaxis with amlodipine

Only two studies have been reported on the prophylaxis with amlodipine. A woman 35-year-old was suffering from migraine, and had 1 or 2 severe headaches a mount, the migraine occurred at menstruation and was treated with amlodipine at the daily dose of 5 mg and this treatment prevented the migraine. A woman 63-year-old suffered from migraine for 33 years, the headaches persisted even after the menopause, and occurred five to six times a month. She was treated with amlodipine at the daily dose of 5 mg and this treatment prevented the migraine.[9] A man 27-year-old was suffering from migraine, developed 4 to 5 episodes of migraine weekly, and he was treated with amlodipine at the daily dose of 10 mg and this treatment prevented the migraine.[10] These results indicate that amlodipine, administered at the daily dose of 5 mg to 10 mg, prevents the migraine.

Treatment of hypertensive patients with amlodipine

Six studies have been reported on the treatment of hypertensive patients with amlodipine. It was compared the efficacy of felodipine to that of amlodipine in lowering the systolic and diastolic blood pressures in hypertensive patients. Felodipine was administered once daily at the dose of 5 mg to 10 mg to 59 hypertensive patients and amlodipine was administered once daily at the dose of 5 mg to 10 mg to 59 hypertensive patients. Felodipine reduced the systolic and diastolic blood pressures by 18 and 13 mmHg, respectively, after 2 weeks of treatment, and by 25 and 15 mmHg, respectively, after 6 weeks of treatment. Amlodipine reduced the systolic and diastolic blood pressures by 16 and 12 mmHg, respectively, after 2 weeks of treatment, and by 23 and 17 mmHg, respectively, after 6 weeks of treatment. The adverse-effects were reported in 13.5% of patients treated with felodipine and in 18.6% of patients treated with amlodipine. The treatment with felodipine was similarly efficacious as that with amlodipine in lowering the systolic and diastolic blood pressures and was well-tolerated.[11] A total of 1,175 hypertensive patients were followed for 4 years and the blood pressure was recorded 6 months before and 12 months after the treatment with amlodipine at the daily dose of 10 mg. The mean systolic and diastolic blood pressures were lowered by 19.6 and 15.5 mmHg, respectively. The treatment with amlodipine lowered the systolic and diastolic blood pressures and was well-tolerated.[12] A total of 737 hypertensive patients were treated with amlodipine at the daily dose of 5 mg to 10 mg. Amlodipine led to a significant reduction in the mean systolic blood pressure by 24.9 mmHg and the mean diastolic pressure was lowered by 14.8 mmHg and this treatment caused few adverse-effects. The treatment with amlodipine lowered the systolic and diastolic blood pressures and was well-tolerated.[13] It was investigated the efficacy of the combination of nebivolol plus amlodipine in lowering the systolic and diastolic blood pressures in hypertensive patients. Nebivolol was administered at the daily dose of 5 mg and amlodipine was co-administered at the daily dose of 5 mg to 10 mg and this treatment caused few adverse-effects. This drug combination lowered the systolic and diastolic blood pressures and was well-tolerated.[14] It was compared the efficacy of amlodipine and that of doxazosin, administered alone or in combination, in lowering the systolic and diastolic blood pressures in 75 hypertensive patients. Amlodipine was administered at the daily dose of 10 mg to 37 hypertensive patients and doxazosin was administered at the daily dose of 4 mg to 38 hypertensive patients and the treatments lasted 6 weeks. The percentage of patients who achieved the target systolic and diastolic blood pressures of < 140 and < 90 mmHg, respectively, was 78.1% when amlodipine and doxazosin were administered alone and it was 94.2% in patients who received amlodipine combined with doxazosin and these treatments did not cause adverse-effects. The combination of amlodipine with doxazosin lowered the systolic and diastolic blood pressures more effectively

(P-value < 0.05) than when amlodipine and doxazosin were administered alone and these treatments were well-tolerated.[15] Amlodipine was administered at the daily dose of 0.12 mg/kg to 0.16 mg/kg to 55 hypertensive children aged 5.4 to 11.5 years. There was an inverse relationship between child age and amlodipine dose. Amlodipine lowered the systolic blood pressure from 129±12 to 122±12 mmHg (P-value = 0.004) and the diastolic blood pressure was lowered from 78±13 to 70±19 mmHg (P-value = 0.004) and this treatment caused few adverse-effects. The treatment with amlodipine lowered the systolic and diastolic blood pressures in hypertensive children and was well-tolerated.[16] These results indicate that amlodipine, administered at the daily dose of 5 mg to 10 mg, effectively lowers the systolic and diastolic blood pressures in hypertensive patients. Amlodipine is affective as felodipine in lowering the systolic and diastolic blood pressures in hypertensive patients and the treatment with amlodipine or with felodipine is well-tolerated. Nebivolol combined with amlodipine lowers the systolic and diastolic blood pressures in hypertensive patients and this drug combination is well-tolerated. The combination of doxazosin with amlodipine lowers the systolic and diastolic blood pressures in hypertensive patients more effectively than wend doxazosin and amlodipine are administered alone. Amlodipine, administered at the daily dose of 0.12 mg/kg to 0.16 mg/kg, lowers the systolic and diastolic blood pressures in hypertensive children.

Trials conducted with amlodipine and with other antihypertensive drugs

Five trials have been reported with amlodipine and with other antihypertensive drugs. A clinical trial compared the efficacy of amlodipine to that of nifedipine in lowering the systolic and diastolic blood pressures. Hypertensive patients were randomly assigned to receive either amlodipine once daily at the dose of 5 mg (N = 257) or nifedipine (N = 248) once daily at the dose of 30 mg and both treatments lasted 4 weeks. At the end of treatment, the systolic and diastolic blood pressures were lowered by 14.1±0.8 and 8.0±0.4 mmHg, respectively, in patients treated with amlodipine and by 14.7±0.8 and 7.8±0.5 mmHg, respectively, in patients treated with nifedipine and both treatments caused few adverse-effects. The treatment with amlodipine was similarly efficacious as that with nifedipine in lowering the systolic and diastolic blood pressures in hypertensive patients and both treatments were well-tolerated.[17] A randomized, double-blind trial was conducted in 11,506 hypertensive patients who received either a combination of 20 mg of benazepril plus 5 mg of amlodipine (N = 5,754) or a combination of 20 mg of benazepril plus hydrochlorothiazide 12.5 mg (N = 5,452) and both drug combinations were administered once daily for 4 weeks. At the end of treatment, the mean systolic and diastolic blood pressures were 131.6 and 73.3 mmHg, respectively, in patients treated with benazepril plus amlodipine and were 132.5 and 74.4 mmHg, respectively, in patients treated with benazepril plus hydrochlorothiazide and both treatments caused few adverse-effects. The combination benazepril plus amlodipine reduced the systolic and diastolic blood pressures as the combination of benazepril plus hydrochlorothiazide and both drug combinations were well-tolerated.[18] A randomized, controlled trial was conducted in 495 hypertensive patients who were clustered into two groups. The patients of the test group (N = 254) received amlodipine at the daily dose of 2.5 mg to 5 mg plus telmisartan at the daily dose of 20 mg to 80 mg plus chlorthalidone at the daily dose of 4.2 mg to 25 mg and the patients of the control group (N = 241) received amlodipine alone at the daily dose of 10 mg and both treatments lasted 8 weeks. At the end of treatment, the endpoint was to assess the change in systolic and diastolic blood pressures. In patients of the test group, the systolic and diastolic blood pressures were reduced by 19.55±14.75 and 17.07±13.92 mmHg, respectively, and in patients of the control group, the systolic and diastolic blood pressures were reduced by 19.55±14.74 and 17.07±13.92 mmHg, respectively. The percentage of patients who achieved target systolic and diastolic blood pressures was 58.33% in patients of the test group and 52.01% in patients of the control group and both treatments caused few adverse-effects. The treatment with the drug combination and that with amlodipine alone were similarly efficacious in lowering the systolic and diastolic blood pressures and both treatments were well-tolerated.[19] A double-blind, multicentre, randomized trial compared the antihypertensive efficacy and safely of the combination of amlodipine plus cilexetil versus amlodipine alone. A total of 80 patients received amlodipine combined with cilexetil and 90 patients received amlodipine alone. The efficacy was assessed by measuring changes in diastolic and systolic blood pressures and the safely was assessed by measuring the incidence of adverse-effects. Patients received either the combination of amlodipine administered at the daily dose of 5 mg plus cilexetil administered at the daily dose of 16 mg or amlodipine alone administered at the daily dose of 5 mg. After 8 weeks of treatment, the diastolic blood pressure decreased by 9.92±0.86 mmHg in patients who received the combination of amlodipine plus cilexetil and by 2.08±0.86 mmHg in patients who received amlodipine alone (P-value < 0.0001). The systolic blood pressure decreased by 14.27±1.39 mmHg in patients who received the combination of amlodipine plus cilexetil and by 2.77±1.39 mmHg in patients who received amlodipine alone (P-value < 0.0001). The adverse-effects occurred in 11.24% of patients who received the combination of amlodipine plus cilexetil and in 5.62% of patients who received amlodipine alone (P-value = 0.1773). The combination of amlodipine plus cilexetil was more efficacy than amlodipine alone in lowering the diastolic and systolic blood pressures and both treatments were well-tolerated.[20] Aliskiren, a direct renin inhibitor, is effective in lowering the blood pressure in hypertensive patients when is combined with amlodipine or with

hydrochlorothiazide. Liu et al.[21] performed a review which included 19 trials involving 13,614 patients. The combination of aliskiren plus amlodipine was significantly more efficacious (P-value < 0.05) than the combination of aliskiren plus hydrochlorothiazide in lowering the systolic blood and the diastolic blood pressures. The number of adverse-effects and the number of withdrawals were similar in patients who received the combination of aliskiren plus amlodipine and in patients who received the combination of aliskiren plus hydrochlorothiazide. The combination of aliskiren plus amlodipine was more efficacious than the combination of aliskiren plus hydrochlorothiazide in lowering the systolic and diastolic blood pressures and both drug combinations were similarly safe. These results indicate that amlodipine is effective as nifedipine in lowering the systolic and diastolic blood pressures in hypertensive patients and the treatment with amlodipine and that with nifedipine is well-tolerated. The combination of benazepril plus amlodipine lowers the systolic and diastolic blood pressures in hypertensive patients as the combination of benazepril plus hydrochlorothiazide and both drug combinations are well-tolerated. The combination of amlodipine plus telmisartan plus chlorthalidone lowers the systolic and diastolic blood pressures in hypertensive patients as amlodipine alone at the daily dose of 10 mg and the treatment with the drug combination and that with amlodipine alone are well-tolerated. The combination of amlodipine plus cilexetil is more efficacious than amlodipine alone, administered at the daily dose of 5 mg, in lowering the systolic and diastolic blood pressures in hypertensive patients and this drug combination and amlodipine alone are well-tolerated. The combination of aliskiren plus amlodipine is more efficacious that the combination of aliskiren plus hydrochlorothiazide in lowering the systolic and diastolic blood pressures in hypertensive patients and the adverse-effects and the number of withdrawals are similar with these two drug combinations.

Metabolism of amlodipine

Zhu et al.[22] studied the metabolism of amlodipine in human liver microsomes. Amlodipine is metabolized by dehydrogenation of its dihydropyridine moiety to a pyridine derivative. The cytochromes that metabolize amlodipine are CYP3A4 and CYP3A5. Ketoconazole is an inhibitor of CYP3A4 and CYP3A5 and CYP3cide is an inhibitor of CYP3A4. Incubation of human liver microsomes with amlodipine in presence of ketoconazole or CYP3cide completely blocked the formation of the pyridine derivative.

Pharmacokinetics of amlodipine

Faulkner et al.[23] studied the pharmacokinetics of amlodipine in 12 healthy volunteers aged 25.8±3.6 years and weighing 66.6±6.3 kg. A single dose of 10 mg of amlodipine was intravenously infused and a single oral dose of 10 mg of amlodipine was administered for 14 days. Table 1 summarizes the pharmacokinetic parameters of amlodipine on the first day of administration after intravenous and oral administration and table 2 summarizes the pharmacokinetic parameters on days 1 and 14 of treatment after oral administration.

Table 1: Pharmacokinetic parameters of amlodipine which have been obtained on the first day of administration after intravenous and oral administration. Values are the mean±SD, by Faulkner et al.[23]

Parameter	Intravenous administration	Oral administration
Peak concentration (ng/ml)	---	5.9±1.2
Time to peak (h)	---	7.6±1.8
AUC (ng/ml*h)	371±69	238±53
Bioavailability (%)	---	64 (range, 52-88)
Total body clearance (ml/min/kg)	7.0±1.3	---
Distribution volume (L/kg)	21.4±4.4	---
Elimination half-life (h)	33.8±5.3	35.7±6.1
Elimination rate constant (h^{-1})	0.021±0.0032	0.020±0.0036

AUC = area under the concentration-time curve.

This table shows that amlodipine is slowly eliminated as the elimination half-life is about 35 hours and the distribution volume of amlodipine is lower than the water volume. Following oral administration the mean bioavailability of amlodipine is 64% suggesting that amlodipine is presystemically eliminated consequently the area under the concentration-time curve of amlodipine is lower after oral than intravenous administration.

Table 2: Pharmacokinetic parameters of amlodipine which have been obtained on days 1 and 14 of treatment following oral administration. Values are the mean±SD, by Faulkner et al.[23]

Parameter	Day 1	Day 14	Ratio day 14/day 1
Peak Concentration (ng/ml)	6.9±2.6	18.1±7.1	2.6 (0.9-5.7)
Time to peak (h)	8.9±3.7	8.7±1.9	---
Trough concentration (ng/ml)	3.3±1.2	11.8±5.3	3.6 (1.6-11.7)
Average concentration (ng/ml)	4.5±1.6	14.5±5.8	3.2 (1.2-7.4)

Elimination half-life (h)	---	44.7±8.6	---
Elimination rate constant (h^{-1})	---	0.016±0.0034	---

This table shows that the peak concentration, the trough concentration, and the average concentration of amlodipine are higher on day 14 than on day 1 of treatment. The elimination half-life of amlodipine is longer than the interval between amlodipine administrations thus amlodipine accumulates in plasma. The time to reach the peak concentration is similar on day 1 and on day 14 of treatment suggesting that the chronic treatment does not alter the absorption of amlodipine.

Interactions of amlodipine with drugs

Five studies have been reported on the interaction of amlodipine with drugs. Simvastatin and amlodipine are metabolized by CYP3A4. Eight patients with hypercholesterolemia and hypertension received 5 mg daily of oral simvastatin followed by 5 mg daily of oral amlodipine and the treatment lasted 4 weeks. Treatment with simvastatin plus amlodipine increased the peak concentration of 3-Hydroxy-3-methylglutaryl-coenzyme A reductase from 9.6±3.7 to 13.7±4.7 ng/ml (P-value < 0.05) and the area under the concentration-time curve of 3-Hydroxy-3-methylglutaryl-coenzyme A reductase from 34.3±16.5 to 43.9±16.6 ng*h/ml (P-value < 0.05). Thus simvastatin affects the pharmacokinetics of amlodipine.[24] Omeprazole and amlodipine are metabolized by CYP3A4. Of 51 patients, 21 patients (41.2%) were omeprazole extensive metabolizers, 18 patients (35.3%) were omeprazole ultra-rapid metabolizers and 12 patients (23.5%) were omeprazole intermediate metabolizers. The antihypertensive effect of amlodipine was higher (P-value < 0.05) in omeprazole intermediate metabolizers than in omeprazole extensive and ultra-rapid metabolizers. Thus the antihypertensive effect of amlodipine is modulated by the genotype of omeprazole.[25] Amlodipine, valsartan, and rosuvastatin are the drugs co-administered for the treatment of hyperlipidaemia accompanied by hypertension. It was studied the drug-drug interaction between amlodipine valsartan and rosuvastatin in healthy male volunteers. Rosuvastatin lowered (P-value < 0.05) the plasma peak concentration and the area under the concentration-time of valsartan whereas rosuvastatin did not affect the pharmacokinetics of amlodipine.[26] Amlodipine is metabolized by CYP3A4 and efavirenz is an inducer of CYP3A4. When efavirenz is co-administered with amlodipine efavirenz decreased the area under the concentration-time curve of amlodipine by 59%.[27] It was studied the drug-drug interaction between tacrolimus and amlodipine in healthy subjects. Tacrolimus and amlodipine are metabolized by CYP3A5 and tacrolimus inhibits the metabolism of amlodipine. Amlodipine was co-administered with tacrolimus and tacrolimus increased the amlodipine clearance by 1.4-fold (P-value = 0.016). Thus dose of amlodipine should be adjusted when amlodipine is co-administered with tacrolimus.[28] These results indicate that simvastatin and amlodipine are metabolized by CYP3A4 and simvastatin affects the pharmacokinetics of amlodipine. Omeprazole and amlodipine are metabolized by CYP3A4. The antihypertensive effect of amlodipine is higher in omeprazole intermediate metabolizers than in omeprazole extensive and ultra-rapid metabolizers thus the antihypertensive effect of amlodipine is modulated by the genotype of omeprazole. Amlodipine, valsartan and rosuvastatin were co-administered and rosuvastatin affects the pharmacokinetics of valsartan whereas valsartan does not affect the pharmacokinetics of amlodipine. Amlodipine is metabolized by CYP3A4 and efavirenz is an inducer of CYP3A4 and efavirenz decreases the area under the concentration-time curve of amlodipine. Tacrolimus and amlodipine are metabolized by CYP3A5 and tacrolimus inhibits the metabolism of amlodipine and increases the clearance of amlodipine.

Toxicity induced by amlodipine

Eight studies have been reported on the toxicity induced by amlodipine. A 15-year-old girl ingested 14 tablets of 10 mg of amlodipine (total 140 mg) and the blood concentration of amlodipine was 2.7 µg/ml and the girl died.[29] A 72-year-old woman with unremarkable medical history presented to the emergency department due to amlodipine overdose after a suicide attempt. Vital signs at hospital presentation were: heart rate (82 beats/min), arterial pressure (72/55 mmHg), and oxygen saturation (98%). Resuscitation was initiated with intravenous infusion of normal saline 0.9%, noradrenaline, and with calcium chloride, while activated charcoal was orally administrated but the blood pressure remained at 70/45 mmHg. Abruptly, she experienced acute pulmonary oedema and was finally intubated. High-dose of insulin was infused to maintain glycaemic hyperinsulinemia and the hemodynamic improvement occurred after 30 min. The systolic blood pressure raised to 95 mmHg, and decongestion was achieved with intravenous furosemide. Eight days later, the patient was weaned from the mechanical ventilation and she was successfully discharged after 14 days of treatment.[30] A patient ingested 450 mg of amlodipine and presented at the hospital with complaints of nausea, multiple episodes of vomiting, and chest discomfort. On arrival to the hospital, the patient had significant hypotension (80/46 mmHg), bradycardia (40 beats/min), and a fall in oxygen saturation (75%). The patient was symptomatically managed with inotropes, intravenous calcium, intravenous fluids, and oxygen supplementation. The patient received plasma in an attempt to remove the inciting agent and finally the patient recovered and left the hospital.[31] A 24-year-old woman with a past history of depression was treated with sertraline and she was presented to the emergency department with nausea, vomiting, and diarrhoea after ingesting 400 to 600 mg of amlodipine and unknown quantities of simvastatin and trazodone. In the emergency department, she was

euthermic with a heart rate of 99 beats/min and with a blood pressure of 72/34 mmHg. She received extensive treatment including dopamine, norepinephrine, followed by vasopressin and phenylephrine, glucagon, and fat emulsion. Finally she recovered and left the hospital.[32] A 28-year-old woman had seizure disorder and depression and she ingested 80 tablets of 5 mg amlodipine (total 400 mg). She presented to the hospital after 23 hours after ingestion the drug and she was managed in the intensive care unit with mechanical ventilation support and intravenous infusion of noradrenalin, adrenalin, insulin-dextrose, and calcium gluconate. Due to refractory hypotension, veno-arterial extracorporeal membrane oxygenation was initiated on the same day. The patient was successfully managed and finally discharged home.[33] A 20-year-old woman ingested high dose of amlodipine and she was admitted to the hospital with complaints of severe breathing difficulty and multiple episodes of vomiting. She underwent chest X-ray, electrocardiogram and blood investigations. The symptoms of amlodipine toxicity were pulmonary oedema, circulatory shock, hypocalcaemia, hypokalaemia, systemic hypotension, and acute kidney injury. She was discharged from the hospital after the symptoms had recovered.[34] A 46-year-old man ingesting 250 mg of amlodipine and he developed progressively worsening dyspnoea over the next 2 days. Subsequent findings from chest X-ray, electrocardiogram, echocardiogram, and cardiac magnetic resonance imaging were consistent with a diffuse myocarditis process and with severe left ventricular systolic dysfunction. The patient was managed with diuretics and after recovering discharged the hospital.[35] A 28-year-old woman took 25 tablets of 5-mg amlodipine (total 125 mg) with intent to self-harm. On presentation to emergency department, she had shock and hypoxia. Arterial blood gas showed type 1 respiratory failure, and chest X-ray showed bilateral homogenous opacities consistent with acute respiratory distress syndrome. The patient was managed in the intensive care unit with non-invasive ventilation support and intravenous infusion of noradrenaline, insulin-dextrose, and calcium gluconate. The patient ultimately made full recovery and left the hospital.[36]

DISCUSSION

Amlodipine: a dihydropyridine is a multiple Ca^{2+} channel blocker approved for clinical use. An increased concentration of cytosolic Ca^{2+} causes increased concentration in both cardiac and vascular smooth muscle cells. In cardiac myocytes, the entry of extracellular Ca^{2+} causes a larger Ca^{2+} release from intracellular stores (Ca^{2+}-induced Ca^{2+} release) and thereby initiates the contraction twitch. In smooth muscle cells, the entry of Ca^{2+} plays a dominant role but the release of Ca^{2+} from the intracellular storage sites also contributes to contraction of vascular smooth muscle, particularly in some vascular beds. Cytosolic Ca^{2+} concentrations can be increased by diverse contractile stimuli in vascular smooth cells. Many hormones and autacoids increase Ca^{2+} influx through so-called receptor-operated channels, whereas increases in external concentration of K^{+} and depolarizing electrical stimuli increase Ca^{2+} influx through voltage-gated or "potential operated" channels. Amlodipine produces its effects by binding to the α_1 subunit of the L-type voltage-gated Ca^{2+} channels and lowering Ca^{2+} flux through the channel. Depolarization of vascular smooth muscle cells depends primarily on the influx of Ca^{2+}. At least three distinct mechanisms may be responsible for contraction of vascular smooth cells. First, voltage-gated Ca^{2+} channels open in response to depolarisation of the membrane, and extracellular Ca^{2+} moves down its electrochemical gradient into the cell. After closure of Ca^{2+} channels, a finite period of time is required before the channels open again in response to a stimulus. Second, agonist-induced contractions that occur with-out depolarization of the membrane result from stimulation of the G_q-phospholipase C (inositol 1,4,5-triphosphate) pathway, resulting in the release of intracellular Ca^{2+} from the sarcoplasmic reticulum. Empting of intracellular Ca^{2+} stores may trigger further influx of extracellular Ca^{2+} (stores-operated Ca^{2+} entry), but its relevance in smooth muscle is unresolved. Third, receptor-operated Ca^{2+} channels allow the entry of extracellular Ca^{2+} in response to receptor occupancy. An increase in cytosolic Ca2+ results in enhanced binding of Ca^{2+} to calmodulin. The Ca^{2+}-calmodulin complex in turn activates myosin light-chain kinase, with resulting phosphorylation of the myosin light chain. Such phosphorylation promotes interaction between actin and myosin and leads to sustained contraction of smooth muscle Ca^{2+} channel blockers inhibit the voltage dependent Ca^{2+} channels in vascular smooth muscle and decreases Ca^{2+} entry. Amlodipine relaxes arterial smooth muscle and thereby decreases arterial resistance, blood pressure, and cardiac afterload.[1] The efficacy and safely of amlodipine have been reviewed. Amlodipine was administered at the dose of 5 mg once daily to patients with average sitting diastolic blood pressure ≥ 95 and ≤ 115 mmHg and the dose was adjusted to 10 mg once daily after 4 weeks of treatment to achieve target diastolic blood pressure ≤ 90 mmHg. This treatment produced significant (P-value < 0.05) falls in systolic and diastolic blood pressures by 23.7 and 17.3 mmHg, respectively, and was found to be safe and well-tolerated[2], amlodipine was administered once daily at the dose of 5 mg for 8 weeks and the amlodipine dose was increased to 10 mg if the target blood pressure $\geq$ 140/60 mmHg or the sitting diastolic blood pressure was not decreased by ≤ 10 mmHg. This treatment effectively lowered the diastolic blood pressure in hypertensive patients and was found to be safe and well-tolerated[3], amlodipine was administered at the daily dose of 5 mg for 6 months to hypertensive patients and 37.8% of patients achieved the therapeutic goal of systolic and diastolic blood pressures of 140 and < 90 mmHg, respectively. There were only 20 adverse-effects, none was related to amlodipine, and this treatment was found to be safe and well-tolerated[4], nifedipine and

amlodipine were administered at the daily dose of 30 mg and 5 mg, respectively, for 8 weeks to hypertensive patients and both drugs were similarly efficacious in lowering the systolic and diastolic blood pressures. The adverse-effects occurred in 8.8% of patients who received nifedipine and in 5.7% of patients who received amlodipine. Nifedipine and amlodipine lowered the systolic and diastolic blood pressures in hypertensive patients and were found to be safe and well-tolerated[5], amlodipine and valsartan were co-administered once daily at the dose of 5 mg and 160 mg, respectively, to hypertensive patients and this treatment lowered the systolic and diastolic blood pressures and was found to be safe and well-tolerated[6], manidipine was administered at the daily dose of 20 mg for 12 weeks to hypertensive patients and amlodipine was administered at the daily dose of 10 mg for 12 weeks to hypertensive patients and both treatments lowered the systolic and diastolic blood pressures. The adverse-effects were lower (P-value = 0.001) in patients who received manidipine. Manidipine was effective as amlodipine in lowering the systolic and diastolic blood pressures and was better tolerated[7], amlodipine was administered at the daily dose of 2.5 mg to 5 mg for 8 weeks to hypertensive patients with renal dysfunction. The target reduction in systolic and diastolic blood pressures was achieved in 80.0% of patients, they were decreased in 11.4% of patients, and they were unchanged in only 8.6% of patients. This treatment was found to be safe and well-tolerated and amlodipine did not accumulate in patients with renal dysfunction.[8] The prophylaxis with amlodipine has been reviewed. Two women were suffering from migraine and were treated with amlodipine at the daily dose of 5 mg and this treatment prevented the migraine[9], a man was suffering from migraine and was treated with amlodipine at the daily dose of 10 mg and this treatment prevented the migraine.[10] The treatment of hypertensive patients with amlodipine has been reviewed. It was compared the efficacy of felodipine to that of amlodipine in lowering the systolic and diastolic blood pressures in hypertensive patients. Felodipine was administered once daily at the dose of 5 mg to 10 mg and amlodipine was administered once daily at the dose of 5 mg to 10 mg. The antihypertensive effect of felodipine and that of amlodipine was higher after 6 than after 2 weeks of treatment. The adverse-effects were reported in 13.5% of patients treated with felodipine and in 18.6% of patients treated with amlodipine and both treatments were well-tolerated. The treatment with felodipine was similarly efficacious as that with amlodipine in lowering the systolic and diastolic blood pressures and both treatments were well-tolerated[11], hypertensive patients were followed for 4 years and the systolic and diastolic blood pressures were recorded 6 months before and 12 months after the treatment with amlodipine administered at the daily dose of 10 mg. The mean systolic and diastolic blood pressures were lowered by 19.6 and 15.5 mmHg, respectively, and this treatment was well-tolerated[12], hypertensive patients were treated with amlodipine at the daily dose of 5 mg to 10 mg and the mean systolic and diastolic blood pressures were decreased by 24.9 and by 14.8 mmHg, respectively, and this treatment was well-tolerated[13], it was investigated the efficacy of nebivolol, administered at the daily dose of 5 mg, combined with amlodipine, administered at the daily dose of 5 mg to 10 mg, to hypertensive patients. This drug combination lowered the systolic and diastolic blood pressures and was well-tolerated[14], it was compared the efficacy of amlodipine and that of doxazosin, administered alone and in combination, in lowering the systolic and diastolic blood pressures in hypertensive patients. Amlodipine was administered at the daily dose of 10 mg and doxazosin was administered at the daily dose of 4 mg and the treatments lasted 6 weeks. The percentage of patients who achieved target systolic and diastolic blood pressures of < 140 and < 90 mmHg was 78.1% when amlodipine and doxazosin were administered alone and was 94.2% when amlodipine was co-administered with doxazosin. The combination of amlodipine with doxazosin lowered the systolic and diastolic blood pressures more effectively (P-value < 0.05) than when amlodipine and doxazosin were administered alone and the treatments were well-tolerated[15], amlodipine was administered at the daily dose of 0.12 mg/kg to 0.16 mg/kg to hypertensive children. This treatment lowered the systolic blood pressure from 129$\pm$12 to 122$\pm$12 mmHg (P-value = 0.004) and the diastolic blood pressure from 78$\pm$12 to 70$\pm$19 mmHg (P-value = 0.004). The treatment with amlodipine lowered the systolic and diastolic blood pressures in hypotensive children and was well-tolerated.[16] The trials conducted with amlodipine and with other antihypertensive drugs have been reviewed. A clinical trial compared the efficacy of amlodipine to that of nifedipine in lowering the systolic and diastolic blood pressures in hypertensive patients. Patients received either amlodipine once daily at the dose of 5 mg or nifedipine once daily at the dose of 30 mg and both treatments lasted 4 weeks. Amlodipine and nifedipine were similarly efficacious in lowering the systolic and the diastolic blood pressures and the treatment with amlodipine and that with nifedipine was well-tolerated[17], a randomized, double-blind trial was conducted in hypertensive patients who received either a combination of 20 mg of benazepril plus 5 mg of amlodipine once daily or a combination of 20 mg of benazepril plus 12.5 mg of hydrochlorothiazide once daily and both drug combinations were administered for 4 weeks. Both drug combinations were similarly efficacious in lowering the systolic and diastolic blood pressures and were well-tolerated[18], a randomized, controlled trial was conducted in hypertensive patients who received either amlodipine at the daily dose of 2.5 mg to 5 mg plus telmisartan at the daily dose of 20 mg to 80 mg plus chlorthalidone at the daily dose of 4.2 mg to 25 mg or amlodipine alone at the daily dose of 10 mg. Both treatments lasted 8 weeks and were similarly efficacious in lowering the systolic and diastolic blood pressures. At the end of treatment, the blood pressure was controlled in 58.33% of patients who received the

drug combination and in 52.01% of patients who received amlodipine alone and both this drug combination and amlodipine alone were well-tolerated[19], a double-blind, multicentre, randomized trial compared the efficacy and safely of a combination of amlodipine, administered at the daily dose of 5 mg plus cilexetil, administered at the daily dose of 16 mg, versus amlodipine alone administered at the daily dose of 5 mg in lowering the diastolic and systolic blood pressures in hypertensive patients. After 8 weeks of treatment, the combination of amlodipine plus cilexetil lowered the diastolic and systolic blood pressures more effectively (P-value < 0.0001) than amlodipine alone. The adverse-effects occurred in 11.24% of patients who received the combination of amlodipine plus cilexetil and in 5.62% of patients who received amlodipine alone (P-value = 0.1773). The combination of amlodipine plus cilexetil was more efficacious than amlodipine alone in lowering the diastolic and systolic blood pressures and both treatments were well-tolerated[20], aliskiren, a direct renin inhibitor, is effective in lowering the systolic and diastolic blood pressures in hypertensive patients when is combined with amlodipine or with hydrochlorothiazide. The combination of aliskiren plus amlodipine was more efficacious (P-value < 0.05) than the combination of aliskiren plus hydrochlorothiazide in lowering the systolic and diastolic blood pressures and both drug combinations were similarly safe.[21] Zhu et al.[22] studied the metabolism of amlodipine in human liver microsomes. Amlodipine is cleared by dehydrogenation of its dihydropyridine moiety to a pyridine derivative and the cytochromes which metabolize amlodipine are CYP3A4 and CYP3A5. Ketoconazole is an inhibitor of CYP3A4 and CYP3A5, and CYP3cide is an inhibitor of CYP3A4. Incubation of human liver microsomes with amlodipine in presence of ketoconazole or CYP3cide completely blocked the formation of pyridine derivative. Faulkner et al.[23] studied the pharmacokinetics of amlodipine in healthy volunteers. A single dose of 10 mg of amlodipine was intravenously infused and a single oral dose of 10 mg of amlodipine was administered for 14 days. Following the intravenous infusion, the elimination half-life of amlodipine was 33.8±5.3 hours. At the 14th day of amlodipine administered orally the elimination half-life of amlodipine was 44.7±8.6 hours. On the first day of amlodipine administration the peak and trough concentrations of amlodipine were 6.9±2.6 and 3.3±1.2 ng/ml, respectively, and after the 14th day of amlodipine administration, the peak and trough concentrations of amlodipine are 18.1±7.1 and 11.8±5.3 ng/ml, respectively. The elimination half-life of amlodipine is longer than the interval between amlodipine administrations thus amlodipine accumulates in plasma. The interaction of amlodipine with drugs has been reviewed. Simvastatin and amlodipine are metabolized by CYP3A4. Patients received 5 mg daily of oral simvastatin followed by 5 mg daily of oral amlodipine and this drug combination increased (P-value < 0.05) the peak concentration and the area under the concentration-time of 3-Hydroxy-3-methylglutaryl-coenzyme A reductase, thus simvastatin affects the pharmacokinetics of amlodipine[24], omeprazole and amlodipine are metabolized by CYP3A4. Some patients were omeprazole intermediated metabolizes, other patients were omeprazole extensive metabolizers, and other patients were omeprazole ultra-rapid metabolizers. The antihypertensive effect of amlodipine was higher (P-value < 0.05) in omeprazole intermediate metabolizers than in omeprazole extensive and ultra-rapid metabolizers, thus the antihypertensive effect of amlodipine is modulated by the genotype of omeprazole[25], it was studied the drug-drug interaction between amlodipine valsartan and rosuvastatin in healthy male volunteers. Rosuvastatin lowered (P-value < 0.05) the plasma peak and the area under the concentration-time of valsartan whereas rosuvastatin did not affect the pharmacokinetics of amlodipine[26], amlodipine is metabolized by CYP3A4 and efavirenz is an inducer of CYP3A4. When efavirenz is co-administered with amlodipine efavirenz decreased the area under the concentration-time curve of amlodipine by 59%[27], it was studied the drug-drug interaction between tacrolimus and amlodipine in healthy subjects. Tacrolimus and amlodipine are metabolized by CYP3A5 and tacrolimus inhibits the metabolism of amlodipine and increased the clearance of amlodipine by 1.4-fold (P-value = 0.016) thus the dose of amlodipine should be reduced when amlodipine in co-administered with tacrolimus.[28] The toxicity induced by amlodipine has been reviewed. A 15-year-old girl ingested 140 mg of amlodipine the blood concentration of amlodipine was 2.7 µg/ml and the girl died[29], a 72-year-old woman ingested an overdose of amlodipine and at hospital presentation the vital signs were: heart rate (82 beats/min), the arterial pressure (72/55 mmHg), and oxygen saturation (98%). The patient received extensive therapy and after 14 days of treatment she was discharged from the hospital[30], a patient ingested 450 mg of amlodipine and on arrival to the hospital the patient had nausea, multiple episodes of vomiting, chest discomfort, a hypotension (80/46 mmHg), bradycardia (40 beats/min), a fall in oxygen saturation (75%) and after extensive therapy the patient left the hospital[31], a 24-year-old woman ingested 400 to 600 mg of amlodipine and on arrival to the hospital she had nausea, vomiting, diarrhoea, the heart rate was 99 bits/min, and the arterial pressure was 72/34 mmHg. She received extensive therapy and finally she left the hospital[32], a 28-year-old woman ingested 400 mg of amlodipine, she had seizure disorder and depression, and after receiving extensive therapy was discharged home[33], a 20-year-old woman ingested high dose of amlodipine and arrival to the hospital she had severe breathing difficulty, multiple episodes of vomiting, pulmonary oedema, circulatory shock, hypocalcaemia, hypokalaemia, systemic hypotension, and acute kidney injury and after extensive therapy she was discharged from the hospital[34], a 46-year-old man ingested 250 mg of amlodipine and he developed progressively worsening dyspnoea over the next 2 days. Extensive investigation showed that he had diffuse myocarditis process, severe

left ventricular, and systolic dysfunction and after extensive therapy he left the hospital[35], and a 28-year-old woman ingested 125 mg of amlodipine and on arrival at the hospital she had shock and hypoxia and after extensive therapy she recovered and let the hospital.[36] These results indicate that intoxication with amlodipine may cause nausea, vomiting, diarrhoea, hypotension, hypocalcaemia, dyspnoea, bradycardia, myocarditis, fall in oxygen saturation, chest discomfort, breathing difficulty, pulmonary oedema, circulatory shock, or kidney injury. These diseases may be cured with extensive therapy but a blood concentration of about 3 µg/ml of amlodipine causes death.

In conclusion, amlodipine, a dihydropyridine, is a multiple Ca^{2+} channel blocker approved for clinical use and lowers the systolic and diastolic blood pressures in hypertensive patients. The efficacy and safely of amlodipine, the prophylaxis with amlodipine, the treatment of hypertensive patients with amlodipine, and the trials conducted with amlodipine and with other antihypertensive drugs have been reviewed. Amlodipine is metabolized by dehydrogenation of its dihydropyridine moiety to a pyridine derivative by CYP3A4 and CYP3A5. Ketoconazole is an inhibitor of CYP3A4 and CYP3A5 and CYP3cide is an inhibitor of CYP3A4 and ketoconazole and CYP3cide block the formation of the pyridine derivative. The pharmacokinetics of amlodipine have been studied in healthy volunteers following single and repeated administrations of 10 mg. Following single administration the elimination half-life of amlodipine is about 35 hours and following repeated administration the elimination half-life of amlodipine is about 45 hours. The elimination half-life of amlodipine is longer than the interval between amlodipine administrations thus the plasma concentration of amlodipine increases with repeated administrations. The interaction of amlodipine with drugs and the toxicity induced by amlodipine have been reviewed. This aim of this study is to review the clinical pharmacology of amlodipine.

Conflict of interests

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria.

This article is a review and drugs have not been administered to men or animals.

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