**Mechanism of Action**

The mechanism by which nifedipine reduces arterial blood pressure involves peripheral arterial vasodilatation and, consequently, a reduction in peripheral vascular resistance. The increased peripheral vascular resistance, an underlying cause of hypertension, results from an increase in arterial tension in the vascular smooth muscle. Studies have demonstrated that the increase in arterial tension reflects an increase in cytosolic free calcium.

**Pharmacokinetics and Metabolism**

Nifedipine distributes into most body tissues and fluids. The drug is metabolized in the liver and 80% of a dose is eliminated unchanged in the urine by renal excretion. The remainder is excreted in the feces in metabolized form, most likely via the biliary route. The renal excretion is reduced in the presence of renal disease.

When nifedipine extended-release tablets are administered as multiples of 30 mg or more than a dose of 30 mg, absorption may be incomplete under the fasting conditions, plasma concentrations are less than 30 mg and 60 mg doses.

When nifedipine extended-release tablets are administered as multiples of 30 mg over a dose range of 30 mg to 90 mg, approximately 85% of the dose is absorbed with the peak plasma concentration for the 90 mg dose given as 3 to 18 mg greater than predicted from the 30 mg and 60 mg doses.

Nifedipine is extensively metabolized to hydroxy- and inactive metabolites accounting for 60% to 80% of the dose excreted in the urine. Only traces (less than 0.1% of the dose) of the unchanged form can be detected in the urine. The remainder is excreted in the fasting state in metabolized form, most likely by a biliary excretion.

Nifedipine is metabolized via the cytochrome P450 3A4 system. Drugs that are known to either inhibit or induce the cytochrome P450 3A4 system may significantly affect the plasma concentrations of nifedipine extended-release tablets.

No studies have been performed with nifedipine extended-release tablets in patients with renal failure; however, based on studies performed with nifedipine immediate-release capsules, clearance of nifedipine extended-release tablets is decreased in the presence of moderate to severe renal impairment (see WARNINGS). The elimination half-life of nifedipine and nifedipine extended-release tablets, administered under fasting conditions, is approximately 115 mg.

When nifedipine extended-release tablets are given immediately after a high fat meal in healthy volunteers, there is an increase of 40% in the peak plasma nifedipine concentration, a prolongation in the time to peak concentration, but no significant change in the AUC. Plasma clearance of nifedipine may be decreased in the presence of alcohol, and nifedipine dose adjustments may be necessary.

**WARNINGS**

**Increased Angina and/or Myocardial Infarction**

Rarely, patients, particularly those who have severe obstructive arterial disease, have had prolonged, unrelieved angina following administration of nifedipine extended-release tablets. The onset of increased angina or myocardial infarction following initiation of nifedipine therapy will not predict this occurrence and on has been reported to increase its severity.

**Hypotension**

**Hypertension**

Hypotension is more likely to occur if dihydropyridine calcium antagonists such as nifedipine are coadministered with tricyclic antidepressants or other antihypertensive agents.

**Hypothermia and/or Hypotension**

Hypothermia and/or hypotension have been reported with the use of nifedipine extended-release tablets in patients with hypothermia or hypotension, respectively. These adverse reactions were reported in patients receiving nifedipine extended-release tablets at doses comparable to those used in clinical trials. Care is needed when nifedipine extended-release tablets are administered to patients with hypothermia or hypotension. Hypothermia and hypotension may be more likely to occur in patients with hypothermia or hypotension who are also sensitive to the effects of hypotension.

**Hypokalemia**

**Hypokalemia**

Hypokalemia has been reported in patients treated with nifedipine extended-release tablets. Hypokalemia has been reported in patients treated with nifedipine extended-release tablets at doses comparable to those used in clinical trials. Care is needed when nifedipine extended-release tablets are administered to patients with hypokalemia. Hypokalemia may be more likely to occur in patients with hypokalemia who are also sensitive to the effects of hypokalemia.

**Hypertension**

Hypertension in patients with severe renal impairment, including patients undergoing dialysis, has been reported in patients treated with nifedipine extended-release tablets. Hypertension may be more likely to occur in patients with severe renal impairment who are also sensitive to the effects of hypertension.

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Hypotension in patients with severe renal impairment, including patients undergoing dialysis, has been reported in patients treated with nifedipine extended-release tablets. Hypertension may be more likely to occur in patients with severe renal impairment who are also sensitive to the effects of hypotension.
Nifedipine is metabolized by CYP3A4. Co-administration of nifedipine 10 mg capsule and 60 mg nifedipine coat-core tablet with fenofibrate, an inducer of CYP3A4, lowered the AUC and Cmax of nifedipine by approximately 70%. Phenoxybenzamine and phentolamine are also inducers of CYP3A. Alternative antihypertensive therapy should be considered in patients taking phentolamine, phenoxybenzamine, and carbamazepine.

**Immunogenic Drugs**

Tacrolimus: Tacrolimus has been shown to be metabolized via the CYP3A system. Nifedipine has been shown to inhibit the metabolism of tacrolimus in vivo. Transient patients on tacrolimus and nifedipine required from 26% to 38% smaller doses than patients not receiving nifedipine. Nifedipine can increase the exposure to tacrolimus. When nifedipine is coadministerated with tacrolimus the blood concentration of tacrolimus should be monitored and a reduction of the dose of tacrolimus considered.

Sildenafil: A single 60 mg dose of nifedipine and a single 10 mg dose of sildenafil oral solution were administered to 24 healthy volunteers. Clinically significant pharmacodynamic drug interactions were not observed.

**Drug Interactions**

**Antacids**

A dose of 40 mg nifedipine given with antacids increases the blood concentration of nifedipine, and the effect is cumulative in the case of repeated doses of antacids. Therefore, nifedipine should be taken at least 1 hour after the ingestion of antacids.

**Drugs with Narrow Therapeutic Index**

**Anticoagulants**

Nifedipine is an inhibitor of P-gp. Thus, nifedipine may increase the serum concentrations of substrates of P-gp like warfarin. Therefore, the prothrombin time should be monitored in patients receiving warfarin concomitantly with nifedipine.

**Oral Antidiabetic Drugs**

Nifedipine is a substrate of P-gp. The oral bioavailability of 60 mg nifedipine (extended release tablets) is reduced by 40% when co-administered with acarbose. Therefore, careful monitoring is required when patients are coadministered with acarbose and nifedipine.

**Sulfonamides**

Nifedipine is a substrate of P-gp. Therefore, the bioavailability of 30 mg nifedipine extended-release tablets is decreased by 30% when co-administered with cyclosporine. Therefore, monitoring is required when patients are coadministered with cyclosporine and nifedipine.

**Warfarin**

Nifedipine is an inhibitor of P-gp. Thus, nifedipine may increase the serum concentrations of substrates of P-gp like warfarin. Therefore, the prothrombin time should be monitored in patients receiving warfarin concomitantly with nifedipine.

**Insulin**

Nifedipine is an inhibitor of P-gp. Thus, nifedipine may increase the serum concentrations of substrates of P-gp like insulin. Therefore, careful monitoring is required when patients are coadministered with insulin and nifedipine.

**Agents of the Adrenergic Nervous System**

Nifedipine is reported to increase urine volume in patients undergoing reflex sympathetic dystrophy. However, the clinical relevance of this finding is unknown.

**ABC Transporters**

Nifedipine is a substrate of P-gp. Therefore, the bioavailability of 60 mg nifedipine (extended release tablets) is decreased by 40% when co-administered with cyclosporine. Therefore, monitoring is required when patients are coadministered with cyclosporine and nifedipine.

**ACE Inhibitors**

Nifedipine is an inhibitor of P-gp. Thus, nifedipine may increase the serum concentrations of substrates of P-gp like ACE inhibitors. Therefore, careful monitoring is required when patients are coadministered with ACE inhibitors and nifedipine.

**CYP3A4 Inhibitors**

Nifedipine is a substrate of P-gp. Therefore, the bioavailability of 60 mg nifedipine (extended release tablets) is decreased by 40% when co-administered with cyclosporine. Therefore, monitoring is required when patients are coadministered with cyclosporine and nifedipine.

**CYP3A4 Inducers**

Nifedipine is not a substrate of P-gp. Therefore, the bioavailability of 60 mg nifedipine (extended release tablets) is not affected when co-administered with ritonavir. Therefore, monitoring is not required when patients are coadministered with ritonavir and nifedipine.

**Protein Binding**

Nifedipine is an inhibitor of P-gp. Thus, nifedipine may increase the serum concentrations of substrates of P-gp like protein binding agents. Therefore, monitoring is required when patients are coadministered with protein binding agents and nifedipine.

**Effects on Other Drugs**

Nifedipine is an inhibitor of P-gp. Thus, nifedipine may increase the serum concentrations of substrates of P-gp like other drugs. Therefore, careful monitoring is required when patients are coadministered with other drugs and nifedipine.

**Fats**

Nifedipine is a substrate of P-gp. Therefore, the bioavailability of 60 mg nifedipine (extended release tablets) is decreased by 40% when co-administered with cyclosporine. Therefore, monitoring is required when patients are coadministered with cyclosporine and nifedipine.

**References**

Nifedipine is an inhibitor of P-gp. Thus, nifedipine may increase the serum concentrations of substrates of P-gp like other drugs. Therefore, careful monitoring is required when patients are coadministered with other drugs and nifedipine.

**Contraindications**

Nifedipine is an inhibitor of P-gp. Thus, nifedipine may increase the serum concentrations of substrates of P-gp like other drugs. Therefore, careful monitoring is required when patients are coadministered with other drugs and nifedipine.