

NEW ZEALAND DATASHEET

Nifehexal

Nifedipine Ph Eur, modified release tablets, 20 mg

Presentation

Pink to light red, 6 mm round, biconvex plain coated tablets. Each tablet contains nifedipine 20 mg. This product is not able to deliver all approved dose regimes. Do not halve tablet.

Uses

Actions

Nifedipine is a cardioprotective coronary treatment agent.

Pharmacotherapeutic group

C08CA05 - Selective calcium channel blockers with mainly vascular effects, dihydropyridine derivatives, nifedipine.

Mechanism of action

Nifedipine is a calcium antagonist of the 1,4-dihydropyridine type. Calcium antagonists reduce the transmembranal influx of calcium ions through the slow calcium channel into the cell. Nifedipine acts particularly on the cells of the myocardium and the smooth muscle cells of the coronary arteries and the peripheral resistance vessels. The contractile processes of vascular smooth muscle are dependent upon calcium ions. Calcium ions enter these cells during depolarisation as slow ionic transmembrane currents. Nifedipine specifically inhibits slow inward calcium ion channels without changing serum calcium concentrations. Nifedipine is a potent relaxant of arterial smooth muscle. It dilates main coronary arteries and arterioles both in normal and in ischaemic myocardial regions without inducing a steal phenomenon.

Pharmacodynamic effects

In the heart nifedipine dilates the coronary arteries, especially the large conductance vessels, even in the free wall segment of partially stenosed areas. Further, nifedipine reduces the vascular smooth muscle tone in the coronary arteries and prevents vasospasm. The final result is an increased poststenotic blood flow and an increased oxygen supply. With long-term use nifedipine can also prevent the development of new atherosclerotic lesions in the coronary arteries.

Nifedipine directly decreases myocardial oxygen consumption. During myocardial fibre depolarisation, elevation of intracellular calcium ion concentration triggers the contractile process and increases the amount of ATP hydrolysed. By inhibiting the transmembrane flux of calcium that enters myocardial cells and hence decreasing intracellular calcium concentration, nifedipine reduces the amount of ATP hydrolysed and thereby decreases the amount of oxygen consumed by the heart. The clinical significance of this is as yet undecided. Unlike beta-blockers, nifedipine does not abolish the responsiveness of the heart to beta-adrenergic stimulation.

Nifedipine reduces myocardial work and the oxygen requirement by lowering peripheral resistance (afterload). As with myocardial cell contraction, regulation of the contraction of vascular smooth muscle is also dependent upon intracellular calcium ion contraction. By reducing the influx of calcium ions into vascular smooth muscle, nifedipine causes relaxation and peripheral vasodilatation. Peripheral vasodilatation reduces the impedance (afterload) against which the heart works. This unloading of the heart indirectly reduces myocardial energy consumption and oxygen requirements. Ventricular emptying is also facilitated by the reduction in impedance.

Nifedipine reduces the smooth muscle tone of the arterioles, thus lowering the increased peripheral resistance and consequently the blood pressure. At the beginning of the nifedipine treatment there may be a transient reflex increase in heart rate and thus in the cardiac output. However, this increase is not enough to compensate for the vasodilation. In addition nifedipine increases sodium and water excretion both in the short-term and long-term use. The blood-pressure-lowering effect of nifedipine is particularly pronounced in hypertensive patients.

In Raynaud's phenomenon nifedipine can prevent or reduce digital vasospasm.

Onset and duration of action

The pharmacological action of nifedipine persists for up to twelve hours after oral administration.

Pharmacokinetics

Absorption

After oral administration nifedipine is rapidly and almost completely absorbed. The absolute bioavailability of nifedipine from Nifehexal is between 50 and 70%. Simultaneous food intake leads to delayed, but not reduced absorption.

Distribution

Nifedipine is highly bound to serum proteins (92 to 98%). Protein binding may be greatly reduced in patients with renal or hepatic impairment.

Biotransformation

After oral administration, nifedipine is almost completely metabolised in the gut wall and in the liver, primarily by oxidative processes. Most of the dose (about 70 to 80%) is excreted via the kidneys in the form of highly water soluble pharmacologically inactive metabolites. The remainder (about 5 to 15%) is excreted via the bile in the faeces, also in a metabolised form. The unchanged substance is recovered only in trace amounts (below 0.1%) from the urine.

Elimination

The terminal elimination half-life is 6 to 12 hours due to delayed absorption. No accumulation of the substance after the usual dose was reported during long-term treatment.

Special patient considerations

In cases of impaired kidney function no substantial changes have been detected in comparison with healthy volunteers. In cases of impaired hepatic function, the elimination half-life is distinctly prolonged and the total clearance is reduced. A dose reduction may be necessary in severe cases.

Indications

Treatment of coronary heart disease: chronic stable angina pectoris (angina of effort); treatment of hypertension.

Dosage and administration

This product is not able to deliver all approved dose regimes. Do not halve tablet.

Dosage

Recommended usual dose

As far as possible the treatment must be tailored to the needs of the individual according to the severity of the disease and the patient's response. Depending on the clinical picture in each case, the basic dose must be introduced gradually. In patients with impaired liver function careful monitoring and, in severe cases, a dose reduction may be necessary.

Dose titration is recommended for hypertensives with severe cerebrovascular disease and for patients, who because of low body weight or multiple therapy with other antihypertensive drugs, are likely to have an excessive reaction to nifedipine. In addition, patients in whom side effects in response to the nifedipine treatment make a finer dose adjustment desirable should be individually stabilised with nifedipine 10 mg. Patients requiring this lower 10 mg dosage should not be treated with Nifehexal 20 mg tablets as they are designed to be swallowed whole and therefore an alternate product should be prescribed.

Unless otherwise prescribed, the following dosage guidelines apply for adults.

Coronary heart disease

Chronic stable angina pectoris (angina of effort) - one 20 mg tablet twice daily (2 x 20 mg/day). If higher dosages are necessary, the dose can be increased in stages up to maximum 60 mg daily.

Hypertension

One 20 mg tablet twice daily (2 x 20 mg/day). If higher dosages are necessary, the dose can be increased in stages up to maximum 60 mg daily. Coadministration with CYP 3A4 inhibitors or CYP 3A4 inducers may result in the recommendation to adapt the nifedipine dose or not to use nifedipine at all (refer to Interactions).

Duration of use

The attending physician will determine the duration of use. Because nifedipine has a pronounced antiischemic and antihypertensive action, it should be discontinued gradually, particularly when high doses are used.

Administration

Tablets are generally swallowed whole with a little liquid, independently of meals. Simultaneous food intake leads to delayed but not reduced absorption. Do not halve tablet.

Grapefruit juice is to be avoided (refer to [Interactions](#)).

The recommended dosage interval for nifedipine modified release tablets is about 12 hours and should not be less than 4 hours.

Contraindications

Known hypersensitivity to nifedipine or to any of the inactive ingredients listed in Further information.

Pregnancy and during breastfeeding

Cardiovascular shock

Within the first eight days after an acute episode of myocardial infarction

Concomitant administration with rifampicin (refer to Interactions)

Warnings and precautions

Warnings

Excessive hypotension

Nifedipine may be used in combination with beta-blocking drugs and other antihypertensive agents, but the possibility of potentiation of existing antihypertensive therapy should be noted. Care must be exercised in patients with very low blood pressure (severe hypotension with systolic pressure less than 90 mm Hg), in cases of manifest heart failure and in the case of severe aortic stenosis.

Increased angina

As with other vasoactive substances, angina pectoris attacks may very rarely occur at the start of the treatment with nifedipine. The occurrence of myocardial infarction has been described in isolated cases, although it was not possible to distinguish this from natural course of the underlying disease.

Beta-blocker withdrawal

Nifedipine has no inherent antiarrhythmic action and therefore gives no protection against any arrhythmias which may result from abrupt withdrawal of beta-blockers. Any such withdrawal of betablockers should be gradual over a period of several days.

Congestive heart failure

The onset of cardiac insufficiency has occasionally been observed with patients whose cardiac reserve is poor or who are receiving large doses of beta-blockers.

Precautions**Peripheral oedema**

Mild to moderate peripheral oedema typically associated with arterial vasodilatation and not due to left ventricular dysfunction, occurs in 1 in 10 patients treated with nifedipine. This oedema occurs primarily in the lower extremities and usually responds to diuretic therapy.

Laboratory tests

Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, AST and ALT have been reported. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms, however cholestasis with or without jaundice has been reported.

Rare instances of allergic hepatitis have been reported. Nifedipine, like other calcium channel blockers, decreases platelet aggregation in vitro. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in nifedipine treated patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Use in diabetes

A possible interference with glucose induced insulin release should be taken into account when treating diabetic patients with nifedipine, but based on extensive experience it is probably more accurate to conclude that nifedipine has no true diabetogenic potential.

Outflow obstruction

Nifedipine should be used with caution in the presence of fixed left ventricular outflow obstruction.

Impaired renal function

Nifedipine should be used with caution in patients with impaired renal function. A dose reduction, particularly in severe cases may be required. Close monitoring of response and metabolic effect should apply.

Impaired hepatic function

Nifedipine should be used with caution in patients with impaired hepatic function. A dose reduction, particularly in severe cases may be required. Close monitoring of response and metabolic effect should apply.

Lactose intolerance

Since this medicinal product contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Pregnancy and lactation

Use in pregnancy

Assigned Category C by the Australian Drug Evaluation Committee. This category includes medicines which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

In common with other calcium channel blockers, nifedipine has the potential to produce foetal hypoxia associated with maternal hypotension. Accordingly, it is contraindicated throughout pregnancy.

Nifedipine has been shown to produce teratogenic findings in rats, mice and rabbits, including digital anomalies, malformation of the extremities, cleft palates, cleft sternum, malformation of the ribs. Digital anomalies and malformation of the extremities are possibly a result of compromised uterine blood flow, but have also been observed in animals treated with nifedipine solely after end of the organogenesis period. Nifedipine administration was associated with a variety of embryotoxic, placentotoxic and foetotoxic effects, including stunted foetuses (rats, mice, rabbits), small placentas and underdeveloped chorionic villi (monkeys), embryonic and foetal deaths (rats, mice, rabbits) and prolonged pregnancy/decreased neonatal survival (rats; not evaluated in other species). All of the doses associated with the teratogenic, embryotoxic or foetotoxic effects in animals were maternally toxic and several times the recommended maximum dose for humans. There are no safety and efficacy data from well-controlled studies in pregnant women.

Use in lactation

Nifedipine passes into the breast milk. As there is no experience of possible effects on infants, breastfeeding should first be stopped if nifedipine treatment becomes necessary during the breastfeeding period.

Effects on fertility

In single cases of *in vitro* fertilisation calcium-antagonists like nifedipine have been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function. In those men who are repeatedly unsuccessful in fathering a child by *in vitro* fertilisation, and where no other explanation can be found, calcium antagonists like nifedipine should be considered as possible causes.

Effects on ability to drive and use machines

This medicine is likely to produce minor or moderate adverse effects. Reactions to nifedipine, which vary in intensity from individual to individual, may impair the ability to drive or operate machinery. This applies particularly at the start of the treatment, on changing the medication and in combination with alcohol.

Other

Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity and carcinogenic potential.

Acute toxicity

Acute toxicity has been investigated in various animal species and the individual results are listed in the following table:

Species	LD50 oral (mg/kg)	LD50 intravenous (mg/kg)
Mouse	494 (421 - 572)*	4.2 (3.8 - 4.6)*
Rat	1022 (950 - 1087)*	15.5 (13.7 - 17.5)*
Rabbit	250 - 500	2 - 3

Species	LD50 oral (mg/kg)	LD50 intravenous (mg/kg)
Cat	~ 100	0.5 - 8
Dog	> 250	2 - 3

* 95 % confidence level

Subacute and subchronic toxicity

Daily oral administration to rats (50 mg/kg body weight) and to dogs (100 mg/kg body weight) over periods of 13 and 4 weeks respectively were tolerated without toxic effects. After intravenous administration dogs tolerated up to 0.1 mg/kg body weight/day for 6 days without damage. Daily intravenous administration of 2.5 mg/kg body weight in rats over a period of 3 weeks was also tolerated without signs of damage.

Chronic toxicity

Dogs tolerated up to 100 mg/kg body weight as a daily oral dose over a period of 1 year without toxic damage. In rats toxic effects occurred at concentrations above 100 ppm in the feed (about 5-7 mg/kg body weight).

Carcinogenicity

A long-term study in rats (2 years) yielded no evidence of a carcinogenic effect of nifedipine.

Mutagenicity

To assess the mutagenic effects the Ames test, the Dominant-lethal-test, and the Micronucleus-test were performed in the mouse. No evidence of a mutagenic effect of nifedipine could be found.

Adverse effects

Nifedipine usage worldwide has shown an overall incidence of adverse effects of about 20%.

Clinical trials data

Percentages stated below indicate the incidence in clinical trials. Adverse effects categorised as common were observed with a frequency below 3% with the exception of oedema (9.9%) and headache (3.9%).

More common reactions - incidence 1% or more

Body as a whole: oedema.

Cardiovascular: palpitation, oedema (peripheral), hypotension, vasodilatation.

General: dizziness (vertigo), flushing, light headedness, numbness, tingling, tiredness.

Gastrointestinal: nausea, vomiting, heartburn, dyspepsia.

Nervous system: headache, weakness.

Less common reactions - incidence from 0.1% to <1%

Body as a whole: malaise, pain.

Auditory and vestibular: tinnitus.

Cardiovascular: angina pectoris, postural hypotension, syncope, tachycardia, chest pain, ischaemia (cerebral, retinal).

Gastrointestinal: constipation, abdominal cramps, gum alterations (gingival hyperplasia), diarrhoea,

dry mouth.

Musculoskeletal system: arthralgia, myalgia.

Hypersensitivity: allergic hepatitis.

Metabolic: hyperglycaemia (transient).

Dermatological: pruritis, urticaria, exanthema, exfoliative dermatitis, skin disorder, sweating.

Nervous system: slight sensations of heat in the face and limbs, acute psychosis, myalgia, tremor, insomnia, nervousness, somnolence, change in optical perception (transient).

Hepatic: transaminase increases, intrahepatic cholestasis.

Renal: acute reversible deteriorations in renal function in patients with chronic renal insufficiency, immune complex glomerulonephritis or nephrotic syndrome, increase in daily urine excretion, blood pressure fall in dialysis patients with malignant hypertension and hypovolaemia.

Respiratory: increased asthmatic symptoms after cessation of therapy in patients with chronic obstructive lung disease, dyspnoea.

Haematological: thrombocytopenia, anaemia, leucopenia, purpura.

Urogenital system: nocturia, polyuria.

Other: gynaecomastia.

Rare reactions - incidence from 0.01% to <0.1%

Body as a whole: abdomen enlarged, allergic reaction, photosensitivity reaction.

Gastrointestinal: flatulence, gastrointestinal disorder, GGTP increased, liver function test abnormal.

Nervous system: hypoesthesia.

Special senses: amblyopia.

Spontaneous reports

The most common adverse drug reactions to nifedipine tablets spontaneously reported (n = 1,652 reports) are listed below.

Very rare reactions - incidence 0.01% or less

Haematological and lymphatic system: agranulocytosis.

Skin and appendages: erythromelalgia.

Severe or life-threatening reactions

Anaphylactic reactions have occurred with nifedipine tablets.

In dialysis patients with malignant hypertension and hypovolaemia a distinct fall in blood pressure can occur as a result of vasodilation.

Nifedipine has, like other members of its class, negative inotropic effects on isolated myocardial

tissue. Such effects have not been seen in intact animals or in humans. Nevertheless, it may theoretically precipitate heart failure. Aggravation of cardiac insufficiency has occasionally been reported in patients with compromised cardiac function or when nifedipine is given in combination with beta-blockers.

Acute pulmonary oedema precipitated by nifedipine in a patient with fixed outflow obstruction has been reported. Care should therefore be taken with patients whose cardiac reserve is poor.

Interactions

Medicines and other pharmacologically active substances

Nifedipine is metabolised via the cytochrome P450 CYP3A4 system, located in the intestinal mucosa and the liver. Drugs that are known to inhibit or induce this enzyme system may therefore alter the first pass or the clearance of nifedipine.

Demonstrated interactions

Antihypertensives

The blood pressure lowering effect of nifedipine may be potentiated by other antihypertensive drugs. Conversely, nifedipine may increase the blood pressure lowering effect of concomitant applied antihypertensives, such as ACE inhibitors, alpha-adrenergic blocking agents, alpha-methyldopa, angiotensin I antagonists, beta-adrenoceptor blockers, diuretics, phosphodiesterase 5 inhibitors and other calcium antagonists.

Beta-blockers and nitrates

Nifedipine may be used in conjunction with nitrates and beta-blocking drugs. When nifedipine is administered simultaneously with beta-blockers, the patient should be carefully monitored, since fairly severe hypotension can occur and deterioration of heart failure is also known to develop in isolated cases.

Cisapride

Simultaneous administration of cisapride and nifedipine may lead to increased plasma concentrations of nifedipine. Blood pressure should be monitored upon co-administration of both drugs, and the nifedipine dose reduced if necessary.

Diltiazem

Diltiazem decreases the clearance of nifedipine and, hence, increases plasma nifedipine levels. Therefore, caution should be exercised when the two drugs are used concomitantly and a reduction in the dose of nifedipine may be necessary.

Digoxin

The simultaneous administration of nifedipine and digoxin can lead to reduced digoxin clearance and hence an increase in the plasma digoxin level. The patient should therefore be checked for symptoms of digoxin overdosage as a precaution and, if necessary, the glycoside dose should be reduced taking account of the plasma digoxin concentration.

H₂-receptor antagonists

Due to its inhibition of cytochrome P450 3A4, cimetidine and, to a lesser extent, ranitidine, elevate the plasma concentration of nifedipine and may potentiate the antihypertensive effect. It is suggested that patients taking both nifedipine and cimetidine should be carefully monitored. In case of hypotension, the dosage of nifedipine should be reduced and the patient should be treated with ranitidine, as the interaction with the drug and nifedipine is less pronounced.

Phenytoin

Phenytoin induces CYP3A4. Co-administration of phenytoin with nifedipine reduces the bioavailability and efficacy of nifedipine. When both drugs are concomitantly administered, the clinical response to nifedipine should be monitored and an increase in the nifedipine dose considered, if necessary. If the dose of nifedipine is increased during co-administration of both drugs, a reduction of the nifedipine

dose should be considered when phenytoin is discontinued.

Quinidine

When nifedipine and quinidine have been administered simultaneously, lowered quinidine levels or, after discontinuation of nifedipine, a distinct increase in the plasma quinidine level have been observed in individual cases. For this reason, when nifedipine is either additionally administered or discontinued, monitoring of the quinidine plasma concentration and, if necessary, adjustment of the dose are recommended. Some authors reported increased plasma levels of nifedipine upon coadministration of both drugs, while others did not observe an alteration in the pharmacokinetics of nifedipine. Therefore, if quinidine is added to existing nifedipine therapy, blood pressure should be monitored and, if necessary, the dose of nifedipine should be reduced.

Quinupristin and dalfopristin

Simultaneous administration of quinupristin or dalfopristin and nifedipine may lead to increased plasma concentration of nifedipine, with the effect varying markedly between individuals. Upon coadministration of both drugs, the blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose considered.

Rifampicin

Rifampicin strongly induces the cytochrome P450 3A4 system, accelerating the metabolism of nifedipine. Since this compromises the efficacy of nifedipine, the use of rifampicin in combination with nifedipine is contraindicated.

Others

Case reports of increased plasma phenytoin and theophylline concentrations due to nifedipine administration have been reported. Nifedipine has also been reported to have a potentiating effect on terbutaline and salbutamol induced bronchodilatation in asthmatic patients.

Theoretical potential interactions

Candesartan cilexetil, irbesartan, doxazosin

The blood pressure lowering effect of these agents may be potentiated by co-administration with nifedipine, so caution should be used in initiating combination therapy. Concomitant administration of irbesartan or doxazosin and nifedipine has no effect on the pharmacokinetics of nifedipine, and concomitant administration of candesartan cilexetil and nifedipine has no effect on the pharmacokinetics of either drug.

Carbamazepine, phenobarbitone

No formal studies have been performed to investigate the potential interaction between nifedipine and carbamazepine or phenobarbitone. As both drugs have been shown to reduce the plasma concentrations of nimodipine, a dihydropyridine calcium channel blocker structurally similar to nifedipine, due to enzyme induction, a decrease in nifedipine plasma concentrations and consequential decrease in efficacy is possible.

Fluoxetine

A clinical study investigating the potential of a drug interaction between nifedipine and fluoxetine has not yet been performed. Fluoxetine has been shown to inhibit *in vitro* the cytochrome P450 3A4 mediated metabolism of nifedipine. Therefore an increase of nifedipine plasma concentrations upon co-administration of both drugs is theoretically possible.

Ketoconazole, itraconazole, fluconazole

A formal interaction study investigating the potential of a drug interaction between nifedipine and these anti-mycotic agents has not yet been performed. Anti-mycotic agents of this class are known to inhibit CYP3A4. When administered orally with nifedipine, a substantial increase in systemic bioavailability of nifedipine is possible. Co-administration of these drugs with nifedipine requires careful monitoring and, if necessary, a reduction in the nifedipine dose should be considered.

Macrolide antibiotics (e.g. erythromycin)

No interaction studies have been carried out between nifedipine and macrolide antibiotics, such as erythromycin. As both nifedipine and erythromycin undergo metabolism by CYP3A4, the potential for drug interaction cannot be ruled out at this stage. Erythromycin is known to inhibit CYP3A4 mediated

metabolism of other drugs, and could increase plasma concentrations of nifedipine if administered concomitantly. Azithromycin, although structurally related to the class of macrolide antibiotic does not demonstrate CYP3A4 inhibition.

Nefazodone

A clinical study investigating the potential of a drug interaction between nifedipine and nefazodone has not yet been performed. Nefazodone is known to inhibit the cytochrome P450 3A4 mediated metabolism of other drugs. Therefore an increase of nifedipine plasma concentrations upon coadministration of both drugs cannot be excluded. When nefazodone is given together with nifedipine, the blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered.

Protease inhibitors

A clinical study investigating the potential interaction between nifedipine and the protease inhibitors amprenavir, indinavir, nelfinavir, ritonavir or saquinavir has not yet been performed. Drugs of this class are known to inhibit the CYP3A4 system. In addition, amprenavir, indinavir, nelfinavir, ritonavir and saquinavir have been shown to inhibit in vitro the CYP3A4 mediated metabolism of nifedipine. When administered together with nifedipine, a substantial increase in plasma concentrations of nifedipine due to a decreased first-pass metabolism and decreased elimination cannot be excluded. Upon coadministration, the blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered.

Sodium valproate

No formal studies have been performed to investigate the interaction of nifedipine with sodium valproate. As sodium valproate has been shown to increase the plasma concentrations of nimodipine, a dihydropyridine calcium channel blocker structurally similar to nifedipine, due to enzyme inhibition, an increase in nifedipine plasma concentrations and consequential increase in efficacy is possible.

Tacrolimus

Tacrolimus is metabolised by CYP3A4. Published data indicate that the dose of nifedipine administered simultaneously with tacrolimus may be reduced in individual cases. Upon coadministration of both drugs, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose should be considered.

Interactions shown not to exist

In drug interaction studies, aspirin, benazepril, cerivastatin, omeprazole, orlistat, pantoprazole, ranitidine, rosiglitazone, talinolol and triamterene hydrochlorothiazide did not have clinically significant effects on the pharmacokinetics of nifedipine. Nifedipine did not have clinically significant effects on the pharmacokinetics of cerivastatin, or on the effect of aspirin 100 mg on platelet aggregation and bleeding time.

Conversely, concomitant administration of nifedipine and ajmaline has no effect on the metabolism of ajmaline. Concomitant administration of nifedipine and debrisoquine has no effect on the metabolic ratio of debrisoquine.

Abnormal laboratory test results

Nifedipine may falsely increase spectrophotometric assay values of urinary vanillylmandelic acid. However, determination by HPLC is unaffected.

Food and alcohol

Concomitant intake of grapefruit juice inhibits the oxidative metabolism of nifedipine causing elevated plasma concentrations and prolonged action of nifedipine due to a decreased first pass metabolism or reduced clearance. Consequently, the blood pressure lowering effect of nifedipine may be increased. After regular intake of grapefruit juice this effect may last for at least 3 days after it was last consumed.

Overdosage

Signs and symptoms

The following signs and symptoms have been observed in cases of severe nifedipine intoxication: disturbances of consciousness to the point of coma, a drop in blood pressure, tachycardic/bradycardic heart rhythm disturbances, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema.

Management

As far as treatment is concerned, elimination of the active substance and the restoration of stable cardiovascular conditions have priority. After oral ingestion thorough gastric lavage is recommended, if necessary in the combination with irrigation of the small intestine. Particularly in cases of intoxication with slow release products such as Nifehexal tablets, elimination must be as complete as possible, including the small intestine, to prevent otherwise inevitable absorption of the active substance. Haemodialysis serves no purpose as nifedipine is not dialysable, but plasmapheresis is advisable (high plasma protein binding, relatively low volume of distribution). Bradycardic heart rhythm disturbances may be treated symptomatically with sympathomimetics, and in life-threatening bradycardic disturbances of heart rhythm, temporary pacemaker therapy may be advisable.

Hypotension, as a result of cardiogenic shock and arterial vasodilatation, can be treated with calcium (10 to 20 ml of calcium gluconate 10 % solution administered slowly intravenously and repeated if necessary). As a result, the serum calcium can reach the upper normal range to slightly elevated levels. If the effects are inadequate, the treatment can be continued with ECG monitoring and additional sympathomimetics if necessary (e.g. isoprenaline 0.2 mg slowly intravenously as a continuous infusion of 5 mcg/ minute). If an insufficient increase in blood pressure is achieved with calcium and isoprenaline, vasoconstricting sympathomimetics such as dopamine or noradrenaline are additionally administered. The dosage of these drugs is determined solely by the effect obtained. Additional liquid or volume must be administered with caution because of the danger of overloading the heart.

Pharmaceutical precautions

Instructions for use/handling

Nifedipine is highly light-sensitive. The specially coated tablets must not be broken or crushed. Tablets should only be removed from the packaging immediately before use.

Incompatibilities

None known.

Special precautions for storage

Store at or below 25°C. Protect from light and moisture.

Medicine classification

Prescription Medicine.

Package quantities

Packs of 60 tablets in cartoned blister strips.

Further information

List of excipients

Microcrystalline cellulose, maize starch, lactose, hydroxypropylmethylcellulose, polysorbate 80, polyethylene glycol, titanium dioxide, magnesium stearate, iron oxide red pigment.

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