PRODUCT MONOGRAPH

Pr NIMOTOP®

(Nimodipine Capsules)

30 mg

For Oral Use

Adjunct in the Management of
Subarachnoid Hemorrhage

Calcium Channel Blocking Agent

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(30 mg Nimodipine Capsules)
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THERAPEUTIC CLASSIFICATION

Adjunct in the Management of Subarachnoid Hemorrhage
Calcium Channel Blocking Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Delayed neurological deterioration secondary to cerebral ischemic deficits is believed to be a major determinant of outcome in patients who survive their initial subarachnoid hemorrhage (SAH). NIMOTOP (nimodipine) is a calcium channel blocker of the dihydropyridine group. It appears to have a more marked effect on the cerebral circulation than on the peripheral circulation. Since it acts on the vascular smooth muscle tone by modifying the contractile process which is dependent upon the movement of extracellular calcium into the cells during depolarization. it was tested in patients with SAH in an effort to improve the neurologic outcome in these patients. Clinical studies with nimodipine support its usefulness as an adjunct in the management of some patients with SAH from ruptured aneurysm by improving their neurologic outcome, particularly in Hunt and Hess grades 1 to 3 patients.

The actual mechanism of the possible beneficial effect of nimodipine is, however, unknown. The original rationale for using nimodipine after SAH was to reduce cerebral arterial spasm, but available evidence indicates that nimodipine does not reduce the incidence or severity of cerebral spasm as seen on angiography.

Nimodipine is rapidly and completely absorbed after oral administration of the capsule. Because of a strong first-pass metabolism in the liver, only about 10% of the unchanged drug enters the systemic circulation. The drug is detectable in plasma 15 minutes after oral administration and peak levels occur within 90 minutes. The earlier elimination half-life is approximately 2 hours indicating the need for frequent dosing, although the terminal half-life is 8 to 9 hours. The absolute bioavailability of nimodipine capsule is approximately 13%. No change in the average maximum and minimum plasma concentration occurred after a repeated oral dosage regimen of three times a day for seven days in volunteers.

Nimodipine is metabolized through the cytochrome P450 system, mainly by the *CYP3A4* isoenzyme.

Nimodipine is 99% bound to serum proteins. Approximately 80% is excreted in the bile and 20% by the kidney. The metabolites of nimodipine are believed to be either inactive or considerably less active than the parent compound.

Age: In a single parallel-group study involving 24 elderly subjects (aged 59-79) and 24 younger subjects (aged 22-40), the observed AUC and C_{max} of nimodipine was approximately 2-fold higher in the elderly population compared to the younger study subjects following oral administration (given as a single dose of 30 mg and dosed to steady-state with 30 mg tid for 6 days). The clinical response to these age-related pharmacokinetic differences, however, was not considered significant (see **PRECAUTIONS: Geriatric Use**).

INDICATIONS AND CLINICAL USE

NIMOTOP (nimodipine) may be useful as an adjunct to improve the neurologic outcome following subarachnoid hemorrhage (SAH) from ruptured intracranial aneurysm.

CONTRAINDICATIONS

Hypersensitivity to nimodipine or to any ingredient of the drug product. For a complete list of ingredients, see **PHARMACEUTICAL INFORMATION: COMPOSITION** section of the Product Monograph.

The concomitant use of oral nimodipine and the antiepileptic drugs phenobarbital, phenytoin, or carbamazepine is contraindicated, as the efficacy of nimodipine capsules could be significantly reduced.

The use of nimodipine in combination with rifampin is contraindicated as the efficacy of nimodipine capsules could be significantly reduced when concomitantly administered with rifampin.

WARNINGS

Administration of NIMOTOP Must Not be by Way of Injection of the Capsule Contents into an IV Line or by Other Parenteral Routes, as Temporally Associated Serious, Life-threatening and Fatal Adverse Events Have Been Reported (see DOSAGE AND ADMINISTRATION).

NIMOTOP (nimodipine) should be used only with great caution when cerebral edema or severely raised intracranial pressure are present. Although treatment with nimodipine has not been shown to be associated with increases in intracranial pressure, close monitoring is recommended in these cases or when the water content of the brain tissue is elevated (generalized cerebral edema).

Caution is required in patients with hypotension (systolic blood pressure lower than 100 mm Hg) (see **Blood Pressure** section below).

NIMOTOP is metabolized via the cytochrome P450 3A4 system. Drugs that are known to either inhibit or induce this enzymatic system may therefore alter the first pass or the clearance of nimodipine. Drugs known to inhibit the cytochrome P450 3A4 system and therefore may lead to increased plasma concentrations of nimodipine are:

- macrolide antibiotics (eg, erythromycin)

- HIV protease inhibitors (eg, ritonavir)
- azole antimycotics (eg, ketoconazole)
- antidepressants (eg, nefazodone and fluoxetine)
- cimetidine
- valproic acid

Upon co-administration with these drugs, blood pressure should be monitored and, if necessary, a reduction of the nimodipine dose should be considered (see **DRUG INTERACTIONS**).

Intestinal pseudo-obstruction (paralytic ileus) has been reported rarely. A causal relationship to NIMOTOP (nimodipine) cannot be ruled out. In three cases, the condition responded to conservative management, but a fourth patient required surgical decompression of the extremely distended colon.

Management of patients with SAH

In view of the potential usefulness of NIMOTOP (nimodipine) in improving the neurologic outcome in some patients with SAH, an early decision (whenever possible within 4 days of the ictus) should be made regarding the use of the drug. Since nimodipine is an adjunct in the management of SAH, an early assessment and a complete management program for the individual patient, including the possible indication of neurosurgery, are imperative.

Blood Pressure

NIMOTOP (nimodipine) has the hemodynamic effects of a calcium channel blocker. In the course of clinical studies in patients with SAH, hypotension was reported in 6.6% of patients with Hunt and Hess grades III to V given 90 mg doses (n = 91), and in 7.5% of patients with grades I and II using 30 to 60 mg doses (n = 255). A fall in blood pressure requiring discontinuation of the drug was reported in 2.2% of the patients in the former group. Hypertensive patients may be more susceptible to a lowering of the blood pressure. Blood pressure should, nevertheless, always be carefully monitored during treatment with nimodipine. The use of nimodipine is, however, not generally recommended in patients taking antihypertensive drugs, including other calcium channel blockers, since it may potentiate the effects of these medications (see **DRUG INTERACTIONS: Blood Pressure Lowering Drugs**).

Inadvertent intravenous administration of the contents of NIMOTOP Capsules has resulted in serious adverse consequences including hypotension, cardiovascular collapse, and cardiac arrest.

Simultaneous intravenous administration of beta blockers can lead to mutual potentiation of negative inotropic effects and even to decompensated heart failure.

Patients with Myocardial Infarction

Since there has not been a study of NIMOTOP in acute myocardial infarction reported, similar effects of NIMOTOP to that of immediate-release nifedipine cannot be excluded in acute myocardial infarction. Immediate-release nifedipine is contraindicated in acute myocardial infarction.

Patients with Unstable Angina

Some clinical trials have shown that treatment with the immediate-release formulation of the dihydropyridine, nifedipine, in this setting increases the risk of myocardial infarction and recurrent ischemia.

PRECAUTIONS

In Vitro Fertilization

In single cases of in vitro fertilization, calcium antagonists have been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function.

Hepatic Dysfunction

The metabolism of nimodipine is decreased in patients with impaired hepatic function. Such patients should be given lower doses of the drug and their blood pressure and pulse should be closely monitored.

Renal Dysfunction

There are insufficient data on patients with impaired renal function. Patients with known renal disease and/or receiving nephrotoxic drugs should have renal function closely monitored during intravenous treatment with nimodipine.

Use in Pregnancy

NIMOTOP (nimodipine) has been shown to have a teratogenic effect in rabbits and to be embryotoxic, causing resorption, stunted growth, and higher incidence of skeletal variations, in rats (for details see **TOXICOLOGY**). The safety of nimodipine with respect to adverse effects on human fetal development has not been established. Nimodipine should, therefore, not be used during pregnancy unless the potential benefits are considered to justify the potential risk to the fetus.

Use in Nursing Mothers

Nimodipine and its metabolites have been shown to appear in human milk at concentrations of the same order of magnitude as corresponding maternal plasma concentrations. Nursing mothers are advised not to breastfeed their babies when taking the drug.

Pediatric Use

The safety and effectiveness of nimodipine in children have not been established.

Geriatric Use

Clinical studies of nimodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dosing for elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Administration with Food

A pharmacokinetic study has shown that the bioavailability of nimodipine capsule is reduced in the presence of an American standard breakfast to about two thirds its value in the fasted condition. Patients should be advised to be consistent in the timing of nimodipine capsule administration with or without food.

Effect on Ability to Drive and Operate Machinery

Reactions to nimodipine, which vary in intensity from individual to individual, can impair the ability to drive or to operate machinery. This is most prevalent at the start of the treatment, upon changing the medication, or in combination with alcohol.

DRUG INTERACTIONS

The concomitant use of oral nimodipine and the antiepileptic drugs phenobarbital, phenytoin, or carbamazepine is contraindicated, as the efficacy of nimodipine capsules could be significantly reduced.

The use of nimodipine in combination with rifampin is contraindicated as the efficacy of nimodipine capsules could be significantly reduced when concomitantly administered with rifampin.

Overview

As with all drugs, care should be exercised when treating patients with multiple medications. Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P450 system, mainly via the *CYP3A4* isoenzyme. Co-administration of nimodipine with other drugs which follow the same route of biotransformation may result in altered bioavailability. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered nimodipine to maintain optimum therapeutic blood levels.

Drugs which are known inhibitors of the cytochrome P450 system and therefore may lead to increased plasma concentrations of nimodipine include: azole antifungals, HIV protease inhibitors, fluoxetine, nefazodone, cimetidine, macrolide antibiotics (eg, erythromycin), quinidine and valproic acid. Upon co-administration of nimodipine with these drugs, blood pressure should be monitored and, if necessary, a reduction of the nimodipine dosage should be

considered. Consumption of grapefruit juice, a *CYP3A4* inhibitor, prior to or during treatment with nimodipine should be avoided.

The extent as well as the duration of interactions should be taken into account when administering nimodipine together with drugs known to be inducers of the cytochrome P450 system. Concomitant use of nimodipine and phenobarbital, phenytoin, carbamazepine, or rifampin is contraindicated (see **CONTRAINDICATIONS**). Other *CYP3A4* inducers include dexamethasone, rifabutin and St John's wort.

Blood Pressure Lowering Drugs

Nimodipine may increase the blood-pressure-lowering effect of concomitantly administered antihypertensives, such as A1-antagonists, ACE inhibitors, alpha-adrenergic blocking agents, methyldopa, beta-blockers, diuretics, PDE5 inhibitors, and other calcium antagonists. If co-administration with these drugs is unavoidable, careful monitoring of the patient is necessary (see **WARNINGS: Blood Pressure**).

In addition to the effect on blood pressure, verapamil and diltiazem are also *CYP3A4* inhibitors and may decrease clearance of nimodipine.

Simultaneous intravenous administration of beta blockers can lead to mutual potentiation of negative inotropic effects and even to decompensated heart failure.

Cytochrome P450

CYP3A4 Inhibitors

Azole Antifungals

A formal interaction study investigating the potential drug interaction between nimodipine and ketoconazole has not been performed. Azole antifungals are known to inhibit the cytochrome P450 3A4 system, and various interactions have been reported for other dihydropyridine calcium antagonists. Therefore, when administered together with oral nimodipine, a substantial increase in systemic bioavailibility of nimodipine due to a decreased first-pass metabolism cannot be excluded.

Cimetidine

A pharmacokinetic study has shown that concurrent administration of cimetidine and oral nimodipine results in an almost doubling of the area under the nimodipine plasma concentration curve and about a 50% increase in the peak nimodipine plasma concentration. Patients receiving the two drugs concomitantly should be watched carefully for the possible exaggeration of the effects of nimodipine. It may be necessary to adjust the dosage of nimodipine.

Fluoxetine

In 39 elderly patients (57-75 years of age) treated with 30 mg nimodipine tid, for at least 3 months, concomitant administration of fluoxetine (20 mg/day for 14 days) resulted in a 50% increase in nimodipine steady-state plasma concentrations. In these patients, fluoxetine plasma concentrations were decreased by approximately 20%, while those of its active metabolite,

norfluxetine, were not significantly affected. In patients receiving fluoxetine, a reduction in nimodipine dosage may be required.

Grapefruit Juice

Published data indicate that through inhibition of cytochrome P450, grapefruit juice can increase plasma levels and augment pharmacodynamic effects of some dihydropyridine calcium channel blockers. As a consequence, the blood-pressure-lowering effect may be increased. This effect may last for at least 4 days after the last ingestion of grapefruit juice. Therefore, consumption of grapefruit juice prior to or during treatment with nimodipine should be avoided.

HIV Protease Inhibitors

No formal studies have been performed to investigate the potential interaction between nimodipine and HIV protease inhibitors. Drugs of this class have been reported to be potent inhibitors of the cytochrome P450 3A4 system. Therefore, the potential for a marked and clinically relevant increase in nimodipine plasma concentrations upon co-administration with these protease inhibitors cannot be excluded.

Macrolide Antibiotics

No interaction studies have been carried out between nimodipine and macrolide antibiotics. Certain macrolide antibiotics are known to inhibit the cytochrome P450 3A4 system and the potential for drug interaction cannot be ruled out. Therefore, macrolide antibiotics should not be used in combination with nimodipine.

Valproic Acid

The simultaneous administration of the anticonvulsant valproic acid can lead to an increase in the plasma nimodipine concentration (see **WARNINGS** and **DRUG INTERACTIONS: Antiepileptic Drugs**).

CYP3A4 Inducers

Antiepileptic Drugs

A pharmacokinetic study in epileptic patients receiving long-term treatment has shown that concurrent administration of oral nimodipine and *CYP450* enzyme-inducer antiepileptic drugs (phenobarbital, phenytoin and/or carbamazepine) reduces the bioavailability of nimodipine by about 80%. In the same study, in those patients receiving sodium valproate and oral nimodipine, the bioavailability of the nimodipine increased by about 50%. Concomitant use of nimodipine and phenobarbital, phenytoin, or carbamazepine is contraindicated (see **CONTRAINDICATIONS**).

Other Drugs

Nortryptyline

In 12 elderly patients (60 - 75 years of age) treated with 30 mg nimodipine tid, for at least 3 months, concomitant administration of nortriptyline of 10 mg tid for 7 days resulted in nonsignificant decreases in nimodipine with $AUC_{(0\text{-}24h)}$ of 10% and C_{max} of 17% at steady state. The pharmacokinetics of nortriptyline were not affected by nimodipine.

Haloperidol

In 12 elderly patients (60-80 years of age) receiving haloperidol with an individual but constant dosing (0.7 -23.0 mg/day depending on individual need) for at least one month, treatment with 30 mg tid nimodipine for 7 days did not affect the pharmacokinetics of haloperidol.

Warfarin

An interaction study with nimodipine and warfarin has shown no clinically significant interactions between these drugs.

Diazepam

An interaction study with nimodipine and diazepam has shown no clinically significant interactions between these drugs.

Alcohol

Concomitant use of alcohol may potentiate the effect of nimodipine of lowering blood pressure and causing dizziness.

ADVERSE EVENTS

The most commonly reported adverse events in double-blind clinical studies for patients receiving 60 mg or 90 mg of nimodipine capsule every four hours (n = 666) were decreased blood pressure (5.0%), nausea (1.1%), bradycardia (0.9%), rash (0.8%), edema (0.6%), and diarrhoea (0.5%). Adverse events reported with a frequency greater than 1% are as follows (by dose):

No. of Patients (%)						
	Nimodipine (dose q4h)					Placebo
Sign/Symptom	0.35 mg/kg (n = 82)	30 mg (n = 71)	60 mg (n = 494)	90 mg (n = 172)	120 mg (n = 4)	(n = 479)
Decreased Blood Pressure	1 (1.2)	0	19 (3.8)	14 (8.1)	2 (50.0)	6 (1.2)
Abnormal liver Function Test	1(1.2)	0	2(0.4)	1(0.6)	0	7(1.5)
Edema	0	0	2 (0.4)	2 (1.2)	0	3 (0.6)
Diarrhea	0	3 (4.2)	0	3 (1.7)	0	3 (0.6)
Rash	2 (2.4)	0	3 (0.6)	2 (1.2)	0	3 (0.6)
Headache	0	1 (1.4)	6 (1.2)	0	0	1 (0.2)
Gastrointestinal Symptoms	2 (2.4)	0	0	2 (1.2)	0	0
Nausea	1 (1.2)	1 (1.4)	6 (1.2)	1 (0.6)	0	0
Dyspnea	1 (1.2)	0	0	0	0	0
EKG Abnormalities	0	1 (1.4)	0	1 (0.6)	0	0
Tachycardia	0	1 (1.4)	0	0	0	0
Bradycardia	0	0	5 (1.0)	1 (0.6)	0	0
Muscle Pain/Cramp	0	1 (1.4)	1 (0.2)	1 (0.6)	0	0

No. of Patients (%)						
	Nimodipine (dose q4h)					Placebo
Sign/Symptom	0.35 mg/kg (n = 82)	30 mg (n = 71)	60 mg (n = 494)	90 mg (n = 172)	120 mg (n = 4)	(n = 479)
Acne	0	1 (1.4)	0	0	0	0
Depression	0	1 (1.4)	0	0	0	0

Adverse events for the 60 mg and 90 mg q4h doses with an incidence of less than 1% at all dosages were hepatitis, itching, diaphoresis, GI hemorrhage, vomiting, thrombocytopenia, anemia, jaundice, hematoma, hyponatremia, decreased platelet count, disseminated intravascular coagulation, deep vein thrombosis, palpitation, hypertension, congestive heart failure, light headedness, dizziness, rebound vasospasm, neurological deterioration, wheezing, and phenytoin toxicity.

In severely ill patients, there was overall increased mortality in the nimodipine group using the 90 mg q4h dose as compared to placebo.

Isolated cases of non-fasting elevated serum glucose levels (0.8%), elevated LDH levels (0.4%), decreased platelet counts (0.3%), elevated BUN (0.3%), elevated alkaline phosphatase levels (0.2%) and elevated SGPT levels (0.2%) have been reported.

Adverse events known to be associated with calcium channel blockers should be appropriately monitored.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Erroneous intravenous administration of the contents of NIMOTOP Capsules has resulted in deaths and serious adverse events including hypotension, bradycardia, cardiovascular collapse, and cardiac arrest.

Symptoms of overdosage would be related to cardiovascular effects and the patients may experience peripheral vasodilation with flushing, headache, and marked systemic hypotension.

Clinically significant hypotension due to NIMOTOP overdosage may require active cardiovascular support and should include close monitoring of cardiac and respiratory function. In the event of acute overdose, treatment with NIMOTOP must be discontinued immediately. Symptoms of acute overdose are marked lowering of blood pressure, tachycardia or bradycardia, and gastrointestinal complaints and nausea.

Emergency measures should be governed by the symptoms. Gastric lavage with addition of charcoal should be considered as an emergency therapeutic measure. If there is a marked fall in blood pressure, dopamine or noradrenaline can be administered intravenously. Since no specific antidote is known, subsequent treatment for other side effects should be aimed at the most prominent symptoms. Since nimodipine is 99% bound to serum protein, dialysis is not likely to be of benefit.

For up-to-date information on the management of a suspected drug overdose, the physician should consider contacting a regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

Administration of NIMOTOP Must Not be by Way of Injection of the Capsule Contents into an IV Line or by Other Parenteral Routes, as Temporally Associated Serious, Life-threatening and Fatal Adverse Events Have Been Reported.

The contents of NIMOTOP capsules must not be administered by intravenous injection or other parenteral routes.

For the management of neurological deficits following subarachnoid hemorrhage (SAH), NIMOTOP (nimodipine) therapy should commence as soon as possible or within 4 days of the diagnosis of SAH.

The recommended dosage of NIMOTOP (nimodipine capsules) is 60 mg (two capsules of 30 mg) administered **orally** every 4 hours for 21 consecutive days after diagnosis of SAH. Doses of up to 90 mg every 4 hours have been used in some patients, although the safety of higher doses in severely ill patients has not been well established (see **ADVERSE EVENTS)**.

If the patient is unable to swallow, the capsule contents may be aspirated into a syringe, emptied into the patient's in-situ naso-gastric tube and washed down the tube with 30 mL normal saline.

The contents of nimodipine capsules must not be administered by intravenous injection or other parenteral routes (see WARNINGS).

Due to the possibility of hydrolysis in high alkaline pH, alkaline mixtures should not be given for 2 hours before or after administering NIMOTOP capsules.

Patients with hepatic insufficiency may have substantially reduced clearance and approximately doubled maximum plasma concentration; accordingly, the dosage should be reduced to one 30 mg NIMOTOP capsule every 4 hours in these patients.

NIMOTOP may be used during anesthesia or surgical procedures. In the event of surgical intervention, administration of NIMOTOP should be continued, with dosages as above, to complete the 21-day period.

Drug effects should be carefully monitored in all patients, particularly if higher doses are used.

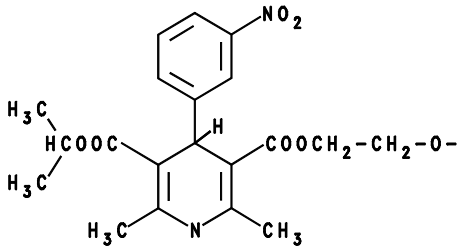
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: nimodipine

Chemical Name: isopropyl-(2-methoxyethyl) 1,4-dihydro-2,6-dimethyl-4(3-nitrophenyl)-3,5-pyridinedicarboxylate

Structural Formula:



Molecular Formula: $C_{21}H_{26}N_2O_7$

Molecular Weight: 418.5

Description: Nimodipine is a pyridine dicarboxylic acid dimethylester. It is a finely crystalline yellow substance with a melting point of 125-126ºC. It is soluble in ethanol, chloroform, ethyl acetate and polyethylene glycol, but insoluble in water.

Nimodipine is stable in neutral and acid media and sensitive to alkalis. It is heat-stable and non-hygroscopic but is moderately sensitive to light, especially in solution.

COMPOSITION

Capsules:

nimodipine
polyethylene glycol 400
peppermint oil
glycerin
gelatin
titanium dioxide

STABILITY AND STORAGE RECOMMENDATIONS

NIMOTOP capsules should be stored in the manufacturer's original foil package at 25ºC, with excursions permitted to 15 to 30ºC. Capsules should be protected from light and freezing.

AVAILABILITY OF DOSAGE FORMS

Each ivory coloured, soft gelatin NIMOTOP (nimodipine) capsule is imprinted with the word NIMOTOP and contains 30 mg of nimodipine. The 30 mg capsules are individually packed in foil and supplied in strips of 100 capsules per carton.

PHARMACOLOGY

Animal Pharmacology

Nimodipine dilates the cerebral vessels and increases cerebral blood flow after intra-arterial (internal carotid artery), intravenous, oral and sublingual administration in several animal species investigated (mouse, rat, rabbit, cat, dog, rhesus and squirrel monkeys). It dilates not only the smaller cerebral vessels, but also larger cerebral arteries such as the basilar artery. The increase in cerebral blood flow is dose-dependent, achieving in the highest dosage a 70% to 100% increase in comparison to the premedication value. The effective dose range is 0.001 to 0.1 mg/kg i.v. and 0.01 to 2.0 mg/kg orally.

Nimodipine is highly lipophilic, allowing it to cross the blood-brain barrier. This was demonstrated after an i.v. injection of titrated nimodipine in the rat.

The increase in peripheral blood flow is less pronounced than in cerebral blood flow after the same dose investigated. In normotensive rats, nimodipine has considerably less tendency to cause a fall in blood pressure than other dihydropyridine calcium channel blockers (e.g. nifedipine and nicardipine). In addition to its dilating effect on the brain vessels in normal animals, the drug prevents the cerebrovascular damage induced by transitory ischemia, by electroshock, anoxia or hypoxia.

In cats, impaired reperfusion of the brain due to a 7 minute global cerebral ischemia was completely prevented by the prophylactic administration of an oral dose of 1 mg/kg, and partially improved by an oral dose of 0.5 mg/kg. The post-ischemic mortality of the animals was drastically reduced by nimodipine. Nimodipine was also effective when administered after the ischemic episode.

In dogs, impaired reperfusion of the brain due to temporary ligastion of the aorta was also prevented by nimodipine. The cerebral blood flow in the delayed post-ischemic hypoperfusion period was nearly doubled by the prophylactic administration of 10 Fg/kg i.v. nimodipine followed by an infusion of 1 Fg/kg/min for two hours prior to the ischemic episode.

The effect of nimodipine was studied on cerebral vasospasm after experimental subarachnoid hemorrhage induced by intracisternal injection of autologous blood in dogs and cats. Angiographic measurements of the cross-sectional areas of the basilar and vertebral arteries of

anaesthetized dogs demonstrated that 0.28 mg/kg sublingual nimodipine reversed the acute cerebral spasm. This occurred without a marked drop in blood pressure (maximum 10% reduction in systolic blood pressure). In a similar study in anaesthetized cats where pial vessel diameters were measured continuously by a Vidicon camera system, 0.01 and 0.1 mg/kg nimodipine i.v. also reversed acute cerebral spasm. The effect of the 0.01 mg/kg dose was more pronounced on pial vessels greater than 100 Fm in diameter than on those less than 100 Fm, whereas the opposite occurred after 0.1 mg/kg nimodipine. Mean arterial blood pressure was reduced by a maximum of 39 mm Hg, 1 minute after injection of 0.01 mg/kg, and subsequently blood pressure gradually returned toward control values. The maximum reduction in mean arterial blood pressure of 60 mm Hg, 1 minute after injection of 0.1 mg/kg was only slightly attenuated over the 30 minute post-nimodipine observation period.

Animal Pharmacokinetics

In rats and dogs C14-labelled nimodipine was absorbed rapidly and completely after oral administration. The maximum plasma concentration was reached after 20 to 60 minutes in rats and 2 to 3 hours in dogs. After maximum plasma concentrations were reached, the radioactivity was eliminated from the plasma with half lives of approximately 40 minutes, 8 hours and 3 days in the rat and 8 hours and 9 days in the dog. A strong first-pass effect was found in rats and only 1% of unchanged substance was present in the plasma 30 minutes after oral administration. In dogs only 7% of the unchanged substance was found 90 minutes after oral administration.

In rats and dogs, 96 to 98% of unchanged active nimodipine was bound to plasma protein. The highest concentrations of nimodipine labelled with C14 were found in the liver and the lowest concentrations in the brain.

Absence of unchanged substance in urine and bile shows that nimodipine was completely eliminated by biotransformation. The excretion of metabolites in both rats and dogs was predominantly in the bile. Eighty-percent of C14 activity administered was found in the faeces and twenty percent in the urine.

In the rat approximately 0.1% of the activity was found in the animal 10 days after oral administration of C14 labelled nimodipine. For the dog, corresponding residual values after 9 days were approximately 0.5% of the administered activity.

TOXICOLOGY

Acute Toxicity Studies

Species	Sex	Route of Administration	LD50 mg/kg	Confidence Limits (p=0.05)
mouse	m	oral	3562	(2746-4417)
mouse	m	i.v.	33	(28-38)
rat	m	oral	6599	(5118- 10033)
rat	m	i.v.	16	(14-18)
rabbit	f	oral	app. 5000	-
rabbit	f	i.v.	app 2.5	-
dog	m/f	oral	1000-2000	-
dog	m/f	i.v.	app 4.0	-

Oral administration caused mild cyanosis, reduced motility and gasping respiration in mice and rats. Intravenous administration produced these symptoms of intoxication, accompanied by tonic-clonic spasms and extension spasms in all the animal species studied.

Subacute Toxicity Studies

In subacute toxicity studies of 3 months duration, oral doses up to 100 mg/kg/day were well tolerated in rats and rhesus monkeys. In dogs, a dose up to 3 mg/kg/day was non-toxic. 10 mg/kg/day caused intolerance reactions, retardation of growth, and pathological changes in P and T waves in the ECG.

Male rats tolerated i.v. nimodipine at dosages of 0.06 and 0.2 mg/kg/day and female rats tolerated dosages of 0.06, 0.2 and 0.6 mg/kg/day. No signs of impairment were noted at these dosages. Nimodipine administered by intravenous drip for 8 hours a day over a period of 4 weeks, at a dose of 150 Fg/kg/H, was well tolerated by beagles and no signs of local or systemic damage were observed.

Chronic Toxicity Studies

In a dog study of one year duration, oral doses of 2.5 mg/kg of nimodipine were well tolerated. At oral doses of 6.25 mg/kg of nimodipine, 3 of 8 animals showed ST segment depression on the electrocardiograms as a manifestation of local disturbance of the blood flow. However, the histopathological examination did not show any indication of myocardial damage.

Reproduction Studies

Nimodipine has been shown to have a teratogenic effect in Himalayan rabbits. Incidence of malformations and stunted fetuses were increased at oral doses (by gavage) of 1 and 10 mg/kg/day administered from day 6 through day 18 of pregnancy, but not at 3.0 mg/kg/day in one of two identical rabbit studies. In the second study an increased incidence of stunted fetuses were seen at 1.0 mg/kg/day, but not at higher doses. Nimodipine was embryotoxic, causing resorption and stunted growth of fetuses, in Long Evans rats at 100 mg/kg/day administered by gavage from day 6 through day 15 of pregnancy. In two other rat studies, doses of 30 mg/kg/day

nimodipine administered by gavage from day 16 of gestation and continued until sacrifice at day 20 of pregnancy or day 21 post-partum, were associated with higher incidence of skeletal variation, stunted fetuses and stillbirths, but no malformations.

Nimodipine did not impair the fertility and general reproductive performance of rats following oral doses of up to 30 mg/kg/day and did not impair 1st and 2nd generation animals.

Carcinogenicity Studies

In a two-year study, higher incidence of adenocarcinoma of the uterus and Leydig-cell adenoma of the testes were observed in rats given a diet containing nimodipine equivalent to 91 to 121 mg/kg/day, than in placebo controls. The differences were, however, not statistically significant and the higher rates of lesions were well within historical control range for these tumors in the Wistar rat strain. Nimodipine was found not to be carcinogenic in a 91-week mouse study, but the high dose of drug in the diet, equivalent to doses of nimodipine as high as 546 to 774 mg/kg/day, shortened the life expectancy of the animals.

Mutagenicity Studies

Mutagenic studies with nimodipine were negative when tested by the Salmonella/microsome test for point mutagenic effects, and by the micronucleus test and by the dominant lethal test.

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