Nisoldipine is a dihydropyridine calcium channel blocker, which reversibly competes with other dihydropyridines for binding to the calcium channel. Like other dihydropyridine calcium channel blockers, nisoldipine has negative inotropic effects on the heart, resulting in dilation of the arterioles. The contractile process of vascular smooth muscle is dependent upon the movement of extracellular calcium into the muscle through specific ion channels, and inhibition of the calcium channel results in dilation of the arterioles.

Nisoldipine has no clinically important chronotropic effects. Except for mild shortening of sinus cycle, SA conduction time, and PR interval, no significant electrophysiological effects were observed with single or multiple doses of nisoldipine. The mechanism of this effect has not been established. In controlled studies of SULAR in patients with angina, this effect was seen about 1.5% of the time in patients given nisoldipine, compared with 0.9% in patients given placebo. Further increases in dosage were associated with a gradual increase in heart rate, regardless of the presence or absence of angina.

Electrophysiologic Effects

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Pharmacodynamics

Pharmacokinetics

Nisoldipine pharmacokinetics are independent of the dose across the clinical dosage range of 17 to 51 mg, with mean terminal half-life of 21 hours. After intravenous administration of nisoldipine, the terminal half-life was 16.2 hours. Nisoldipine is highly metabolized; 5 major urinary metabolites have been identified. Although 60-80% of an oral dose is metabolized, the metabolic pathways are not well characterized. Nisoldipine is highly metabolized by the liver and, in patients with hepatic insufficiency, plasma concentrations of nisoldipine may be expected to be higher than in normal subjects. The mean terminal half-life (reflecting post absorption clearance of nisoldipine) ranges from 13.7 ± 4.3 hours. After oral administration, the plasma at concentrations approximately equal to the parent compound, appears to be the only active metabolite, and its pharmacokinetic properties are similar to those of the parent drug. SULAR pharmacokinetics are independent of the dose, with mean terminal half-life of 21 hours. After intravenous administration of SULAR, the terminal half-life was 16.2 hours. Nisoldipine is highly metabolized; 5 major urinary metabolites have been identified. Although 60-80% of an oral dose is metabolized, the metabolic pathways are not well characterized. Nisoldipine is highly metabolized by the liver and, in patients with hepatic insufficiency, plasma concentrations of nisoldipine may be expected to be higher than in normal subjects. The mean terminal half-life (reflecting post absorption clearance of nisoldipine) ranges from 13.7 ± 4.3 hours. After oral administration, the plasma at concentrations approximately equal to the parent compound, appears to be the only active metabolite, and its pharmacokinetic properties are similar to those of the parent drug.

Although acute hemodynamic studies of nisoldipine in patients with NYHA Class II-IV heart failure were consistent with the drug's effects on peripheral vascular resistance, its effects on ventricular function, particularly in combination with a beta-blocker, have not been studied. Therefore, no conclusions can be made about the use of nisoldipine in patients with heart failure.

Pharmacokinetic factors that could affect the disposition of nisoldipine include age, hepatic and renal function, and drug interactions.

Hepatic Insufficiency: In patients with liver cirrhosis given a dose bioequivalent to 8.5 mg SULAR, plasma concentrations of nisoldipine were 5-fold higher than those in normal subjects. Nisoldipine pharmacokinetics were linear in this study; therefore, dosage adjustment is not necessary for patients with liver cirrhosis.

Renal Insufficiency: In normal volunteers with creatinine clearance of 40 mL/min (the upper limit of normal), steady-state plasma concentration increased about 5 and 16 times the MRHD when compared on a mg/m2 basis. In pregnant rabbits, decreased fetal and placental weight was observed at both 30 and 100 mg/kg/day. These doses are, respectively, about 5 and 16 times the MRHD when compared on a mg/m2 basis. In a study in which pregnant monkeys (both treated and control) had high rates of abortion and mortality, the only adverse effects seen were at 30 mg/kg/day. The dosage of nisoldipine in pregnant women should not exceed the MRHD when compared on a mg/m2 basis.

Nisoldipine was neither teratogenic nor fetotoxic at doses that were not maternally toxic. In pregnant rabbits, decreased fetal and placental weight was observed at both 30 and 100 mg/kg/day. These doses are, respectively, about 5 and 16 times the MRHD when compared on a mg/m2 basis. In pregnant monkeys (both treated and control) had high rates of abortion and mortality, the only adverse effects seen were at 30 mg/kg/day. The dosage of nisoldipine in pregnant women should not exceed the MRHD when compared on a mg/m2 basis.

Pharmacokinetic Interactions

Most antihypertensive drugs may be considered to interact in some way with other drugs administered concurrently. With nisoldipine, no clinically important interactions have been found with other antihypertensive agents, digoxin, or warfarin. No antianginal effects of nisoldipine antagonism have been observed.

Although acute hemodynamic studies of nisoldipine in patients with NYHA Class II-IV heart failure were consistent with the drug's effects on peripheral vascular resistance, its effects on ventricular function, particularly in combination with a beta-blocker, have not been studied. Therefore, no conclusions can be made about the use of nisoldipine in patients with heart failure.

Antihypertensive activity is attributed to its effect on peripheral vascular resistance. The mechanism for the antihypertensive activity of nisoldipine appears to be independent of the renin-angiotensin-aldosterone system or on plasma norepinephrine concentration in normals. Changes in blood pressure and left ventricular ejection fraction. A study of the immediate release formulation showed no effect of nisoldipine on systolic or diastolic blood pressure in normals.
Adverse Event Placebo 8.5 mg 17 mg 25.5 mg 34 mg

libido, depression, hypesthesia, hypertonia, insomnia, nervousness, paresthesia, somnolence, tremor, vertigo

Nervous: abnormal dreams, abnormal thinking and confusion, amnesia, anxiety, ataxia, cerebral ischemia, decreased

Musculoskeletal: arthralgia, arthritis, leg cramps, myalgia, myasthenia, myositis, tenosynovitis

gain, weight loss

Metabolic and Nutritional: gout, hypokalemia, increased serum creatine kinase, increased nonprotein nitrogen, weight

Digestive: abnormal liver function tests, anorexia, colitis, diarrhea, dry mouth, dyspepsia, dysphagia, flatulence, (flattening, inversion, nonspecific changes), venous insufficiency

Extrasystoles, supraventricular tachycardia, syncope, systolic ejection murmur, T wave abnormalities on ECG

Peripheral 10 7 15 20 27

Rash 2 1

Nausea 2 1

Body As A Whole: cellulitis, chills, facial edema, fever, flu syndrome, malaise

established, they are listed to alert the physician to a possible relationship with SULAR treatment.

or with unspecified incidence in other studies. Although a causal relationship of SULAR to these events cannot

The following adverse events occurred in 1% of all patients treated for hypertension in U.S. and foreign clinical trials,