

Clinical studies of nicardipine 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 the elderly and younger patients. In general, use low initial doses in elderly patients, reflecting the greater hefrequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

10. OVERDOSAGE

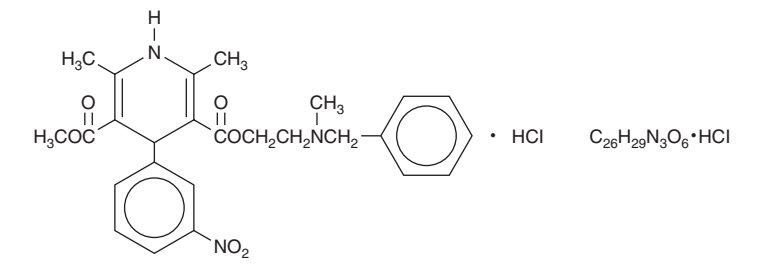
Several overdosages with orally administered nicardipine have been reported. One adult patient allegedly ingested 600 mg of immediate-release oral nicardipine, and another patient, 2160 mg of the sustained-release formulation of nicardipine. Symptoms included marked hypotension, bradycardia, palpitations, flushing, drowsiness, confusion and slurred speech. All symptoms resolved without sequelae. An overdosage occurred in a one year old child who ingested half of the powder in a 30 mg nicardipine standard capsule. The child remained asymptomatic.

Based on results obtained in laboratory animals, lethal overdose may cause systemic hypotension, bradycardia (following initial tachycardia) and progressive atrioventricular conduction block. Reversible hepatic function abnormalities and sporadic focal hepatic necrosis were noted in some animal species receiving very large doses of nicardipine.

For treatment of overdosage, implement standard measures including monitoring of cardiac and respiratory functions. Position the patient so as to avoid cerebral anoxia. Use vasopressors for patients exhibiting profound hypotension.

11. DESCRIPTION

Cardene (nicardipine hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium channel blocker). Cardene I.V. Premixed Injection for intravenous administration contains 40 mg of nicardipine hydrochloride per 200 mL (0.2 mg/mL) in either dextrose or sodium chloride. Nicardipine hydrochloride is a dihydropyridine derivative with IUPAC (International Union of Pure and Applied Chemistry) chemical name (+)-2-(benzyl-methyl amino) ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate monohydrochloride and has the following structure:



Nicardipine hydrochloride is a greenish-yellow, odorless, crystalline powder that melts at about 169°C. It is freely soluble in chloroform, methanol, and glacial acetic acid, sparingly soluble in anhydrous ethanol, slightly soluble in *n*-butanol, water, 0.01 M potassium dihydrogen phosphate, acetone, and dioxane, very slightly soluble in ethyl acetate, and practically insoluble in benzene, ether, and hexane. It has a molecular weight of 515.99.

Cardene I.V. Premixed Injection is available as a ready-to-use sterile, non-pyrogenic, clear, colorless to yellow, iso-osmotic solution for intravenous administration in a 200 mL GALAXY container with 40 mg (0.2 mg/mL) nicardipine hydrochloride in either dextrose or sodium chloride.

Cardene I.V. Premixed Injection in 5.0% Dextrose

40 mg in 200 mL (0.2 mg/mL)

Each mL contains 0.2 mg nicardipine hydrochloride, 50 mg dextrose hydroxide, USP, 0.0384 mg citric acid, anhydrous, USP. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH to 3.7 to 4.7.

Cardene I.V. Premixed Injection in 0.83% Sodium Chloride

40 mg in 200 mL (0.2 mg/mL)

Each mL contains 0.2 mg nicardipine hydrochloride, 8.3 mg sodium chloride, USP, 0.0384 mg citric acid, anhydrous, USP, and 3.84 mg sorbitol, NF. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH to 3.7 to 4.7.

The GALAXY container is fabricated from multilayered plastic (PL 2501). Solutions are in contact with the polyethylene layer of the container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability and safety of the plastic have been confirmed in tests in animals according to the USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nicardipine inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle without changing serum calcium concentrations. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. The effects of nicardipine are more selective to vascular smooth muscle than cardiac muscle. In animal models, nicardipine produced relaxation of coronary vascular smooth muscle at drug levels which cause little or no negative inotropic effect.

12.2 Pharmacodynamics

Hemodynamics

Cardene I.V. produces significant decreases in systemic vascular resistance. In a study of intra-arterially administered Cardene I.V., the degree of vasodilation and the resultant decrease in blood pressure were more prominent in hypertensive patients than in normotensive volunteers. Administration of Cardene I.V. to normotensive volunteers at dosages of 0.25 to 3.0 mg/hr for eight hours produced changes of <5 mmHg in systolic blood pressure and <3 mmHg in diastolic blood pressure.

An increase in heart rate is a normal response to vasodilation and decrease in blood pressure; in some patients these increases in heart rate may be pronounced. In placebo-controlled trials, the mean increases in heart rate were 7 ± 1 bpm in postoperative patients and 8 ± 1 bpm in patients with severe hypertension at the end of the maintenance period.

Hemodynamic studies following intravenous dosing in patients with coronary artery disease and normal or moderately abnormal left ventricular function have shown significant increases in ejection fraction and cardiac output with no significant change, or a small decrease, in left ventricular end-diastolic pressure (LVEDP). There

is evidence that Cardene increases blood flow. Coronary dilatation induced by Cardene I.V. improves perfusion and aerobic metabolism in areas with chronic ischemia, resulting in reduced lactate production and augmented oxygen consumption. In patients with coronary artery disease, Cardene I.V., administered after beta-blockade, significantly improved systolic and diastolic left ventricular function.

In congestive heart failure patients with impaired left ventricular function, Cardene I.V. increased cardiac output both at rest and during exercise. Decreases in left ventricular end-diastolic pressure were also observed. However, in some patients with severe left ventricular dysfunction, it may have a negative inotropic effect and could lead to worsened failure.

“Coronary steal” has not been observed during treatment with Cardene I.V. (Coronary steal is the detrimental redistribution of coronary blood flow in patients with coronary artery disease from underperfused areas toward better perfused areas.) Cardene I.V. has been shown to improve systolic shortening in both normal and hypokinetic segments of myocardial muscle. Radionuclide angiography has confirmed that wall motion remained improved during increased oxygen demand. (Occasional patients have developed increased angina upon receiving oral nicardipine. Whether this represents coronary steal in these patients, or is the result of increased heart rate and decreased diastolic pressure, is not clear.)

In patients with coronary artery disease, Cardene I.V. improves left ventricular diastolic distensibility during the early filling phase, probably due to a faster rate of myocardial relaxation in previously underperfused areas. There is little or no effect on normal myocardium, suggesting the improvement is mainly by indirect mechanisms such as afterload reduction and reduced ischemia. Cardene I.V. has no negative effect on myocardial relaxation at therapeutic doses. The clinical benefits of these properties have not yet been demonstrated.

Electrophysiologic Effects

In general, no detrimental effects on the cardiac conduction system have been seen with Cardene I.V. During acute electrophysiologic studies, it increased heart rate and prolonged the corrected QT interval to a minor degree. It did not affect sinus node recovery or SA conduction times. The PA, AH, and HV intervals* or the functional and effective refractory periods of the atrium were not prolonged. The relative and effective refractory periods of the His-Purkinje system were slightly shortened.

*PA = conduction time from high to low right atrium; AH = conduction time from low right atrium to His bundle deflection, or AV nodal conduction time; HV = conduction time through the His bundle and the bundle branch-Purkinje system.

Hepatic Function

Because the liver extensively metabolizes nicardipine, plasma concentrations are influenced by changes in hepatic function. In a clinical study with oral nicardipine in patients with severe liver disease, plasma concentrations were elevated and the half-life was prolonged [*see Warnings and Precautions (5.4)*]. Similar results were obtained in patients with hepatic disease when Cardene I.V. (nicardipine hydrochloride) was administered for 24 hours at 0.6 mg/hr.

Renal Function

When Cardene I.V. was given to mild to moderate hypertensive patients with moderate degrees of renal impairment, significant reduction in glomerular filtration rate (GFR) and effective renal plasma flow (RPF) was observed. No significant differences in liver blood flow were observed in these patients. A significantly lower systemic clearance and higher area under the curve (AUC) were observed.

When oral nicardipine (20 mg or 30 mg TID) was given to hypertensive patients with impaired renal function, mean plasma concentrations, AUC, and C_{24hr} were approximately two-fold higher than in healthy controls. There is a transient increase in electrolyte excretion, including sodium [*see Warnings and Precautions (5.5)*].

Acute bolus administration of Cardene I.V. (2.5 mg) in healthy volunteers decreased mean arterial pressure and renal vascular resistance; glomerular filtration rate (GFR), renal plasma flow (RPF), and the filtration fraction were unchanged. In healthy patients undergoing abdominal surgery, Cardene I.V. (10 mg over 20 minutes) increased GFR with no change in RPF when compared with placebo. In hypertensive type II diabetic patients with nephropathy, oral nicardipine (20 mg TID) did not change RPF and GFR, but reduced renal vascular resistance.

Pulmonary Function

In two well-controlled studies of patients with obstructive airway disease treated with oral nicardipine, no evidence of increased bronchospasm was seen. In one of the studies, oral nicardipine improved forced expiratory volume 1 second (FEV₁) and forced vital capacity (FVC) in comparison with metoprolol. Adverse experiences reported in a limited number of patients with asthma, reactive airway disease, or obstructive airway disease are similar to all patients treated with oral nicardipine.

12.3 Pharmacokinetics

Distribution

Rapid dose-related increases in nicardipine plasma concentrations are seen during the first two hours after the start of an infusion of Cardene I.V. Plasma concentrations increase at a much slower rate after the first few hours, and approach steady state at 24 to 48 hours. The steady-state pharmacokinetics of nicardipine are similar in elderly hypertensive patients (>65 years) and young healthy adults. On termination of the infusion, nicardipine concentrations decrease rapidly, with at least a 50% decrease during the first two hours post-infusion. The effects of nicardipine on blood pressure significantly correlate with plasma concentrations. Nicardipine is highly protein bound (>95%) in human plasma over a wide concentration range.

Following infusion, nicardipine plasma concentrations decline tri-exponentially, with a rapid early distribution phase (α-half-life of 2.7 minutes), an intermediate phase (β-half-life of 44.8 minutes), and a slow terminal phase (γ-half-life of 14.4 hours) that can only be detected after long-term infusions. Total plasma clearance (Cl) is 0.4 L/hr•kg, and the apparent volume of distribution (V_d) using a non-compartment model is 8.3 L/kg. The pharmacokinetics of Cardene I.V. are linear over the dosage range of 0.5 to 40.0 mg/hr.

Metabolism and Excretion

Cardene I.V. has been shown to be rapidly and extensively metabolized by the liver. Nicardipine does not induce or inhibit its own metabolism and does not induce or inhibit hepatic microsomal enzymes.

After coadministration of a radioactive intravenous dose of Cardene I.V. with an oral 30 mg dose given every 8 hours, 49% of the radioactivity was recovered in the urine and 43% in the feces within 96 hours. None of the dose was recovered as unchanged nicardipine.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Rats treated with nicardipine in the diet (at concentrations calculated to provide daily dosage levels of 5, 15, or 45 mg/kg/day) for two years showed a dose-dependent

increase in thyroid hyperplasia and neoplasia (follicular adenoma/carcinoma). One- and three-month studies in the rat have suggested that these results are linked to a nicardipine-induced reduction in plasma thyroxine (T4) levels with a consequent increase in plasma levels of thyroid stimulating hormone (TSH). Chronic elevation of TSH is known to cause hyperstimulation of the thyroid.

In rats on an iodine deficient diet, nicardipine administration for one month was associated with thyroid hyperplasia that was prevented by T4 supplementation. Mice treated with nicardipine in the diet (at concentrations calculated to provide daily dosage levels of up to 100 mg/kg/day) for up to 18 months showed no evidence of neoplasia of any tissue and no evidence of thyroid changes.

There was no evidence of thyroid pathology in dogs treated with up to 25 mg nicardipine/kg/day for one year and no evidence of effects of nicardipine on thyroid function (plasma T4 and TSH) in man.

There was no evidence of a mutagenic potential of nicardipine in a battery of genotoxicity tests conducted on microbial indicator organisms, in micronucleus tests in mice and hamsters, or in a sister chromatid exchange study in hamsters.

No impairment of fertility was seen in male or female rats administered nicardipine at oral doses as high as 100 mg/kg/day (human equivalent dose about 16 mg/kg/day, 8 times the maximum recommended oral dose).

13.3 Reproductive and Developmental Toxicology

Embryotoxicity, but no teratogenicity, was seen at intravenous doses of 10 mg nicardipine/kg/day in rats and 1 mg/kg/day in rabbits. These doses in the rat and rabbit are equivalent to human IV doses of about 1.6 mg/kg/day and 0.32 mg/kg/day respectively. (The total daily human dose delivered by a continuous IV infusion ranges from 1.2 to 6 mg/kg/day, depending on duration at different infusion rates ranging from 3 to 15 mg/hr as individual patients are titrated for optimal results.) Nicardipine was also embryotoxic when administered orally to pregnant Japanese White rabbits, during organogenesis, at 150 mg/kg/day (a dose associated with marked body weight gain suppression in the treated doe), but not at 50 mg/kg/day (human equivalent dose about 16 mg/kg/day or about 8 times the maximum recommended human oral dose). No adverse effects on the fetus were observed when New Zealand albino rabbits were treated orally, during organogenesis, with up to 100 mg nicardipine/kg/day (a dose associated with significant mortality in the treated doe). In pregnant rats administered nicardipine orally at doses of up to 100 mg/kg/day (human equivalent dose about 16 mg/kg/day) there was no evidence of embryotoxicity or teratogenicity. However, dystocia, reduced birth weight, reduced neonatal survival and reduced neonatal weight gain were noted.

14. CLINICAL STUDIES

Effects In Hypertension

In patients with mild to moderate chronic stable essential hypertension, Cardene I.V. (0.5 to 4.0 mg/hr) produced dose-dependent decreases in blood pressure. At the end of a 48-hour infusion at 4.0 mg/hr, the decreases were 26.0 mmHg (17%) in systolic blood pressure and 20.7 mmHg (20%) in diastolic blood pressure. In other settings (e.g., patients with severe or postoperative hypertension), Cardene I.V. (5 to 15 mg/hr) produced dose-dependent decreases in blood pressure. Higher infusion rates produced therapeutic responses more rapidly. The mean time to therapeutic response for severe hypertension, defined as diastolic blood pressure ≤95 mmHg or ≥25 mmHg decrease and systolic blood pressure ≤160 mmHg, was 77 ± 5.2 minutes. The average maintenance dose was 8.0 mg/hr. The mean time to therapeutic response for postoperative hypertension, defined as ≥15% reduction in diastolic or systolic blood pressure, was 11.5 ± 0.8 minutes. The average maintenance dose was 3.0 mg/hr.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Cardene I.V. Premixed Injection is supplied as a single-use, ready-to-use, iso-osmotic solution for intravenous administration in a 200 mL GALAXY container with 40 mg (0.2 mg/mL) nicardipine hydrochloride in either dextrose or sodium chloride.

Pack Size	Diluent	NDC Number
10 bags, each containing 40 mg in 200 mL (0.2mg/mL)	5% Dextrose	NDC 24477-324-02
10 bags, each containing 40 mg in 200 mL (0.2mg/mL)	0.83% Sodium Chloride	NDC 24477-323-02

16.2 Storage and Handling

Store at controlled room temperature 20° to 25°C (68° to 77°F), refer to USP Controlled Room Temperature.

Protect from freezing. Avoid excessive heat. Protect from light, store in carton until ready to use.

Manufactured by: Baxter Healthcare Corporation Deerfield, IL 60015 USA	Marketed by: EKR Therapeutics, Inc. Bedminster, NJ 07921 USA
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To report an adverse event, record the lot number and call Drug Safety at 1-877-207-5802.

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