findings, however, have been observed in normals or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Electrophysiologic Effects: Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

ADVERSE EFFECTS:
Calcium-channel blockers are normally avoided in patients with heart failure but amlodipine has not been found to have any adverse effects on morbidity or mortality in patients with severe heart failure receiving drug. Therefore it may be suitable treatment for angina pectoris or hypertension in some patients.

Amlodipine is well tolerated by most patients. In clinical trials in adults, the rate of discontinuation (1.5%) was no different than that of placebo. The most commonly reported adverse effects were headache (in 7.3% of patients), edema (1.8 to 10.8%), dizziness (1.1 to 3.4%), flushing (0.7 to 2.7%) and palpitations (0.7 to 4.5%). Other adverse effects reported in 1 to 4% of patients receiving either amlodipine or placebo include: fatigue, nausea, abdominal pain, somnolence. Muscle cramps, pruritus and rash. The incidence of hypotension, arrhythmias and peripheral ischemia with amlodipine use was less than 1%. In post marketing surveillance, gynecomastia and hepatic dysfunction (with jaundice and elevated hepatic transaminases) have been reported.

In pediatric reports, amlodipine has been associated with the development of edema, fatigue, flushing, headache, dizziness and nausea.

DRUG INTERACTIONS:
The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance.

NOTE: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Anesthetics, hydrocarbon inhalation: on current use with amlodipine may produce additive hypotension although calcium channel blocking agents may be useful to prevent supraventricular tachycardias, hypertension, or coronary spasm during surgery, caution is recommended during use.

Anti-inflammatory drugs, nonsteroidal (NSAIDs) especially indomethacin : NSAIDs may reduce the antihypertensive effects of amlodipine by inhibiting renal prostaglandin synthesis and/or causing sodium and fluid retention.

Beta-adrenergic blocking agents :although reports of adverse effects resulting from concurrent use of amlodipine with the beta-adrenergic blocking agents are lacking, caution is recommended given the similarity of amlodipine to nifedipine; concurrent use of nifedipine with the beta-adrenergic blocking agents, although usually well-tolerated, may produce excessive hypotension and, in rare cases, may increase the possibility of congestive heart failure.

Estrogens : estrogen-induced fluid retention may tend to increase blood pressure the patients should be carefully monitored to confirm that the desired effect is being obtained.

Highly protein-bound medications such as:
Anticoagulants,coumarin – and indandione-derivatives,
Anticonvulsants, hydantoin,
Anti-inflammatory drugs, nonsteroidal
Quinine
Salicylates
Sulfinpyrazone

caution is advised when these medications are use concurrently with amlodipine since amlodipine is highly protein bound; changes in serum concentrations of the free, unbound medications may occur.

Hypotension-producing medications : antihypertensive effects may be potentiated when amlodipine is used concurrently with hypotension-producing medications; although some antihypertensive and/or diuretic combinations are used concurrently, dosage adjustments may be necessary.

Lithium: concurrent use with amlodipine potentially may result in neurotoxicity in the form of nausea, vomiting, diarrhea, ataxia, tremors and/or tinnitus; caution is recommended.

Sympathomimetics : concurrent use may reduce antihypertensive effects of amlodipine; the patient should be carefully monitored to confirm that the desired effect is being obtained.

MEDICAL CONSIDERATION/CONTRAINDICATIONS:

Except under special circumstances, this medication should not be used when the following medical problem exists:

Hypotension (severe) : amlodipine may aggrevate this condition

RISK – BENEFIT SHOULD BE CONSIDERED WHEN THE FOLLOWING MEDICAL PROBLEMS EXIST:

Aortic stenosis : increased risk of heart failure because of fixed impedance to flow across the aortic valve.

Congestive heart failure: amlodipine should be used with caution because of the slight risk for negative inotropic effect.

Hepatic function impairment – clearance of amlodipine may be reduced since it undergoes extensive hepatic metabolism; elimination half-life may be prolonged to 60 hours.

Sensitivity to amlodipine.

PATIENT MONITORING:

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition);
> blood pressure determinations
> ECG readings
> Heart rate determinations
> Reduced frequency or severity of anginal attacks
Decreased nitrate consumption
Improved exercise tolerance without angina recommended primarily during dosage titration or when dosage is increased from established maintenance dosage level; also recommended when other medications are added that affect cardiac conduction or blood pressure.

Blood pressure determinations are recommended at periodic intervals to monitor efficacy and safety of amlodipine therapy; selected patients may be trained to perform blood pressure measurements at home and reports the results at regular physician visits.

CARCINOGENICITY:
No evidence of carcinogenicity was revealed in studies with rats and mice given amlodipine at dosages of 0.5, 1.25 and 2.5mg per kg of body weight (mg/kg) per day for 2 years.

MUTAGENICITY:
No evidence of mutagenicity was observed at the gene or chromosome level.

PREGNANCY/REPRODUCTION:
Fertility- No impairment of fertility was observed in rats given amlodipine at doses 8 times the maximum recommended human dose prior to mating.

Pregnancy- Studies have not been done in humans.
No evidence of teratogenecity or other embryo/fetal toxicity was observed in rats or rabbits given up to 10mg/kg during periods of major organogenesis. However, the number of intrauterine deaths increased above five-fold and rat litter size was significantly decreased (by 50%).

Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

LABOR:
Amlodipine has been shown to prolong the duration of labor in rats.

BREAST-FEEDING:
It is not known whether amlodipine is distributed in breast milk thus it is recommended that nursing be discontinued while amlodipine is administered.

PEDIATRICS:
No information is available on the relationship of age to the effects of amlodipine in pediatric patients. Safety and efficacy have not been established.

GERIATRICS:
The half-life of amlodipine may be increased in the elderly. These patients may be more sensitive to the hypotensive effects of amlodipine and may require a lower initial dose.

DENTAL:
Gingival hyperplasia is a rare side effect that has been reported with amlodipine. It has been reported with other calcium channel blocking agents, such as diltiazem, felodipine, verapamil and, most commonly, nifedipine. It usually starts as gingivitis or gum inflammation in the first 1 to 9 months of treatment. Resolution of the hyperplasia and improvement of the clinical symptoms usually occur one to four weeks after discontinuation of therapy. A strictly enforced program of professional teeth cleaning combined with plaque control by the patient will minimize growth rate and severity of gingival enlargement. Periodontal surgery may be indicated in some cases and should be followed by careful plaque control to inhibit recurrence of gum enlargement.

SURGICAL:
Recent evidence suggest that withdrawal of antihypertensive therapy prior to surgery may be undesirable. However, the anesthesiologist must be aware of such therapy.