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VERAPAMIL HYDROCHLORIDE INJECTION USP
(Verapamil Hydrochloride)

2.5 mg/mL

2 and 4 mL Ampoules and Vials

Antiarrhythmic
PRESCRIBING INFORMATION

NAME OF DRUG

PRVERAPAMIL HYDROCHLORIDE INJECTION USP
(Verapamil Hydrochloride)

2.5 mg/mL

2 and 4 mL Ampoules and Vials

THERAPEUTIC CLASSIFICATION

Antiarrhythmic

ACTION AND CLINICAL PHARMACOLOGY

Verapamil, a synthetic papaverine derivative, is believed to exert its antiarrhythmic effects by selective inhibition of transmembrane fluxes of calcium in cardiac muscle, coronary and systemic arteries and in cells of the intracardiac conduction system. The drug blocks the transmembrane influx of calcium through the slow channel without affecting, to any significant degree, transmembrane influx of sodium through the fast channel. This results in a reduction of free calcium ions available within these cells.

Electrical activity through the sinoatrial (SA) and atrioventricular (AV) nodes depends, to a significant degree, upon calcium influx through the slow channel. By inhibiting this influx, verapamil slows AV conduction and prolongs the effective refractory period within the AV node in a rate-related manner. This effect results in a reduction of the ventricular rate in patients with atrial flutter and/or atrial fibrillation and a rapid ventricular response. By interrupting re-entry at the AV node, verapamil can restore normal sinus rhythm in patients with paroxysmal supraventricular tachycardias (PSVT), including Wolff-Parkinson-White (W-P-W) syndrome. Verapamil has no effect on conduction across accessory bypass tracts.

Verapamil does not alter the normal atrial action potential or intraventricular conduction time, but depresses amplitude, velocity of depolarization, and conduction in depressed atrial fibers.

Verapamil has a local anesthetic action that is 1.6 times that of procaine on an equimolar basis. It is not known whether this action is important at the doses used in man.

Verapamil does not alter total serum calcium levels.

Hemodynamics:

Verapamil reduces afterload and myocardial contractility. In most patients, including those with organic cardiac disease, the negative inotropic action of verapamil is countered by reduction of afterload, and cardiac index is usually not reduced. However, in patients with moderately severe to severe cardiac
dysfunction (pulmonary wedge pressure above 20 mm Hg, ejection fraction less than 30%), acute worsening of heart failure may be seen.

After a single IV injection of verapamil, hemodynamic effects peak within 5 minutes and persist for 10-20 minutes; effects on the AV node occur within 1-2 minutes, peak at 10-15 minutes, and persist for 10-20 minutes. Effects on the AV node may persist for as long as 6 hours.

The commonly used intravenous doses of 5 - 10 mg verapamil produce transient, usually asymptomatic, reduction in normal systemic arterial pressure, systemic vascular resistance and contractility; left ventricular filling pressure is slightly increased.

Pharmacokinetics:

Following intravenous infusion in man, verapamil is eliminated bi-exponentially with a rapid early distribution phase (t½ about 4 minutes) and a slower terminal elimination phase (t½ 2-5 hours). Intravenously administered verapamil has been shown to be rapidly metabolized.

In healthy men, orally administered verapamil undergoes extensive first pass metabolism in the liver with 12 metabolites having been identified. The metabolism of verapamil is mediated by cytochrome P450 enzymes. The major metabolites have been identified as various N- and O-dealkylated products of verapamil. The two main metabolic routes of verapamil are N dealkylation and N-demethylation. N-dealkylation is mediated by CYP 3A4 and CYP 1A2 isoenzymes of the cytochrome P450 system. CYP 3A4 is also responsible for verapamil's N demethylation which results in the formation of norverapamil. Only norverapamil is present in plasma in more than trace amounts. Nor possesses 20% of the cardiovascular activity of the parent compound.

Approximately 70% of an administered dose is excreted in the urine and 16% in the feces within 5 days. About 3-4% is excreted as unchanged drug.

Approximately 90% of verapamil is bound to plasma proteins.

Neither verapamil nor norverapamil can be removed by hemodialysis.

**INDICATIONS AND CLINICAL USE**

**VERAPAMIL HYDROCHLORIDE INJECTION, USP** may be used in:

- Rapid conversion to sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory bypass tracts (Wolff-Parkinson-White [W-P-W] and Lown-Ganong-Levine [L-G-L] syndromes). When clinically advisable, appropriate vagal maneuvers (e.g. Valsalva maneuver) should be attempted prior to administration of verapamil hydrochloride.

- Temporary control of rapid ventricular rate in atrial flutter or atrial fibrillation except when the atrial flutter and/or atrial fibrillation are associated with accessory bypass tracts (Wolff Parkinson-White [W-P-W] and Lown-Ganong-Levine [L-G-L] syndromes).

Because a small fraction (<1%) of patients treated with verapamil respond with life threatening adverse responses (rapid ventricular rate in atrial flutter/fibrillation and accessory bypass tract, marked hypotension, or extreme bradycardia/asystole) (see **CONTRAINDICATIONS** and **WARNINGS**), the use
of intravenous verapamil should, if possible, be in a treatment setting with monitoring and resuscitation facilities, including DC cardioversion capability (see SYMPTOMS AND TREATMENT OF OVERDOSAGE). Cardioversion has been used safely and effectively after intravenous verapamil.

CONTRAINDICATIONS

VERAPAMIL HYDROCHLORIDE INJECTION, USP is contraindicated in:

1. Acute myocardial infarction
2. Severe hypotension or cardiogenic shock
3. Second- or third-degree AV block (except in patients with a functioning artificial ventricular pacemaker)
4. Sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker)
5. Severe congestive heart failure (unless secondary to a supraventricular tachycardia amenable to verapamil hydrochloride therapy)
6. Concomitant use of injectable verapamil hydrochloride with beta-blockers and cardiac depressant drugs.

The use of intravenous verapamil hydrochloride with these drugs can produce a reduction in myocardial contractility. This myocardial depressant effect (independent of changes in heart rate) can be significant in patients with impaired left ventricular performance.

On rare occasions the concomitant administration of intravenous beta-blockers and intravenous verapamil hydrochloride has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure or recent myocardial infarction.

Accordingly intravenous verapamil hydrochloride and intravenous beta-adrenergic blocking drugs should not be administered in close proximity to each other (i.e. within a few hours).

7. Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g., Wolff-Parkinson-White, Lown-Ganong-Levine syndromes) are at risk to develop ventricular tachyarrhythmia including ventricular fibrillation if verapamil hydrochloride is administered.

8. Ventricular tachycardia: Administration of intravenous verapamil hydrochloride to patients with wide-complex ventricular tachycardia (QRS ≥ 0.12 sec) can result in marked hemodynamic deterioration and ventricular fibrillation. Proper pretherapy diagnosis and differentiation from wide-complex supraventricular tachycardia is imperative in the emergency room setting.

9. Known hypersensitivity to verapamil hydrochloride.

WARNINGS

VERAPAMIL HYDROCHLORIDE INJECTION, USP SHOULD BE GIVEN AS A SLOW INTRAVENOUS INJECTION OVER AT LEAST A TWO-MINUTE PERIOD OF TIME UNDER CONTINUOUS ECG AND BLOOD PRESSURE MONITORING (see DOSAGE AND ADMINISTRATION).
Heart Failure

When heart failure is not severe or rate related, it should be controlled with digitalis glycosides and diuretics, as appropriate, before verapamil hydrochloride is used. In patients with moderately severe to severe cardiac dysfunction (pulmonary wedge pressure above 20 mm Hg, ejection fraction less than 30%), acute worsening of heart failure may be seen.

Because of the drug's negative inotropic effect, verapamil hydrochloride should not be used in patients with poorly compensated congestive heart failure, unless the failure is complicated by or caused by arrhythmia. If it is used in such patients, they must be digitalized prior to treatment. Continuous monitoring is mandatory when i.v. verapamil hydrochloride is used in digitalized patients. It has been reported that digoxin plasma levels may increase with chronic oral administration of verapamil hydrochloride (see WARNINGS - Concomitant Antiarrhythmic Therapy).

Hypotension

Severe hypotension has occasionally occurred following i.v. administration of verapamil hydrochloride. On rare occasions, this has been followed by loss of consciousness. If severe hypotension develops, verapamil hydrochloride should be promptly discontinued and vasoconstrictor substances started. Intravenous verapamil hydrochloride often produces a decrease in blood pressure below baseline levels that is usually transient and asymptomatic, but may result in dizziness. Administration of calcium chloride, or calcium gluconate prior to intravenous administration of verapamil hydrochloride may prevent this hemodynamic response (see SYMPTOMS AND TREATMENT OF OVERDOSAGE).

In patients using antihypertensive drugs, the additional hypotensive effect should be taken into consideration.

Bradycardia/Asystole

Verapamil hydrochloride slows conduction across the AV node and rarely may produce second or third degree AV block, bradycardia and in extreme cases, asystole. This is more likely to occur in patients with a sick sinus syndrome (SA nodal disease), which is more common in older patients (see CONTRAINDICATIONS).

The total incidence of bradycardia (ventricular rate less than 60 beats/min.) was 1.2% in controlled studies. Asystole in patients other than those with sick sinus syndrome is usually of short duration (few seconds or less) with spontaneous return to AV nodal or normal sinus rhythm. If this does not occur promptly, appropriate treatment should be initiated immediately (see SYMPTOMS AND TREATMENT OF OVERDOSAGE).

Heart Block

Verapamil hydrochloride prolongs AV conduction time. While high-degree AV block has not been observed in controlled clinical trials in the United States, a low percentage (less than 0.5%) has been reported in the world literature. Development of second-or third-degree AV block or unifascicular, bifascicular, or trifascicular bundle branch block requires reduction in subsequent doses or discontinuation of verapamil hydrochloride and institution of appropriate therapy, if needed (see SYMPTOMS AND TREATMENT OF OVERDOSAGE).
**Ventricular Fibrillation**

Intravenous administration of verapamil hydrochloride may precipitate ventricular fibrillation. Patients with atrial flutter/fibrillation and an accessory AV pathway (e.g. Wolff-Parkinson-White or Lown-Ganong-Levine syndromes) may develop increased antegrade conduction across the aberrant pathway bypassing the AV node, producing a very rapid ventricular response after receiving verapamil hydrochloride or digitalis. This has been reported in approximately 1% of the patients treated with verapamil hydrochloride. Treatment is usually DC cardioversion. Cardioversion has been used safely and effectively after intravenous verapamil hydrochloride (see **SYMPTOMS AND TREATMENT OF OVERDOSAGE**).

**Impaired Hepatic and Renal function**

Because verapamil is extensively metabolized in the liver, decreased dosage should be used in patients with hepatic insufficiency.

Approximately 70% of an administered dose of verapamil hydrochloride is excreted as metabolites in the urine. Therefore, verapamil should be used cautiously in patients with impaired renal function. Patients with impaired hepatic and/or renal function should be monitored carefully for abnormal prolongation of PR interval, blood pressure changes or other signs of excessive pharmacologic effects.

Significant hepatic and/or renal failure should not increase the effects of a single intravenous dose of verapamil hydrochloride but may prolong its duration. Repeated intravenous injections of verapamil hydrochloride in such patients may lead to accumulation and an excessive pharmacologic effect of the drug. If repeated injections are essential, blood pressure and PR interval should be carefully monitored and smaller repeat doses should be utilized.

Verapamil is not removed by hemodialysis.

**Duchenne's Muscular Dystrophy**

Intravenous verapamil hydrochloride can precipitate respiratory muscle failure in these patients and should, therefore, be used with caution.

**Increased Intracranial Pressure**

Intravenous verapamil hydrochloride has been seen to increase intracranial pressure in patients with supratentorial tumors at the time of anesthesia induction. Caution should be taken and appropriate monitoring performed.

**Concomitant Antiarrhythmic Therapy**

**Digitalis Glycosides:** Intravenous verapamil hydrochloride has been used concomitantly with digitalis preparations without the occurrence of serious adverse effects. However, since both drugs slow AV conduction, patients should be monitored for AV block or excessive bradycardia.

Verapamil hydrochloride produces a significant increase in serum digoxin concentration. This effect is dose dependent and occurs with continued administration of verapamil hydrochloride. As digoxin toxicity may therefore occur, the dose of digoxin may need downward adjustment in patients who are receiving verapamil hydrochloride concomitantly.
Lidocaine: Two deaths have been reported in patients receiving both verapamil hydrochloride and lidocaine intravenously.

Beta-adrenergic Blockers: On rare occasions the concomitant administration of verapamil hydrochloride with beta-blockers has resulted in severe adverse effects, especially in patients with severe cardiomyopathy, congestive heart failure or recent myocardial infarction (see CONTRAINDICATIONS).

Asymptomatic bradycardia (36 beats/min) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a beta-adrenergic blocker) eyedrops and oral verapamil hydrochloride.

Verapamil hydrochloride gives no protection against the danger of abrupt beta-blocker withdrawal. Any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Disopyramide: Disopyramide should not be administered concomitantly with verapamil hydrochloride because of the possibility of additive effect and impairment of left ventricular function.

In patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction who were given oral disopyramide concomitantly with intravenous verapamil hydrochloride, serious adverse effects have occurred.

Disopyramide should not be administered within 48 hours before or 24 hours after verapamil hydrochloride administration.

Procainamide: Intravenous verapamil hydrochloride has been administered to a small number of patients receiving oral procainamide without the occurrence of serious adverse effects.

Quinidine: Intravenous verapamil hydrochloride has been administered to a small number of patients receiving oral quinidine without the occurrence of serious adverse effects. However, several patients have been described in whom the combination resulted in an exaggerated hypotensive response presumably from the combined ability of both drugs to antagonize the effects of catecholamines on alpha-adrenergic receptors. Caution should therefore be used when employing this combination of drugs.

Flecainide: A study in healthy volunteers showed that the concomitant administration of flecainide and verapamil hydrochloride have additive effects on myocardial contractility, AV conduction, and repolarization. Concomitant therapy with flecainide and verapamil hydrochloride may result in additive negative inotropic effect and prolongation of atrioventricular conduction.

PRECAUTIONS

Because a small fraction (<1%) of patients treated with verapamil hydrochloride respond with life-threatening adverse responses (rapid ventricular rate in atrial flutter/fibrillation and accessory bypass tract, marked hypotension, or bradycardia/asystole (see CONTRAINDICATIONS and WARNINGS), the use of VERAPAMIL HYDROCHLORIDE INJECTION intravenously should be in a treatment setting with monitoring and resuscitation facilities, including DC-cardioversion capability (see SYMPTOMS AND TREATMENT OF OVERDOSE).

Cardioversion has been used safely and effectively after intravenous verapamil hydrochloride.
Sick Sinus Syndrome

Precaution should be taken when treating any supraventricular arrhythmia on an emergency basis as it may be caused by an undiagnosed Sick Sinus Syndrome (see CONTRAINDICATIONS and WARNINGS - Bradycardia/Asystole).

Premature Ventricular Contractions

During conversion to normal sinus rhythm, or marked reduction in ventricular rate, a few benign complexes of unusual appearance (sometimes resembling premature ventricular contractions) may be seen after treatment with verapamil hydrochloride. Similar complexes are seen during spontaneous conversion of supraventricular tachycardias, after DC cardioversion and other pharmacologic therapy. These complexes appear to have no clinical significance.

Use in Pregnancy

There are no studies in pregnant women. In all patients of child bearing potential, anticipated benefit must be weighed against possible hazards.

Preliminary studies have shown that unchanged verapamil crosses the placental barrier.

Labour and Delivery

There have been few controlled studies to determine whether the use of verapamil hydrochloride during labour or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labour or increases the need for forceps delivery or other obstetric intervention. Such adverse experiences have not been reported in the literature, despite a long history of use of intravenous verapamil in Europe in the treatment of cardiac side effects of beta-adrenergic agonists used to treat premature labour. Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery.

Use in Nursing Mothers

Verapamil is excreted in human milk. Because of the potential for adverse reactions in nursing infants from verapamil, nursing should be discontinued while verapamil hydrochloride is administered.

Use in Children

Controlled studies with verapamil hydrochloride have not been conducted in pediatric patients. However, uncontrolled experience in more than 250 children (about 50% under 12 months of age and about 25% newborn) indicates that the results of treatment are similar to those in adults. However, in rare instances, severe hemodynamic side effects, some of them fatal, have occurred following the intravenous administration of verapamil hydrochloride in neonates and infants. Caution should therefore be used when administering verapamil hydrochloride to this group of pediatric patients.

Drug Interactions

As with all drugs, care should be exercised when treating patients with multiple medications. Calcium channel blockers undergo biotransformation by the cytochrome P450 system. Coadministration of verapamil hydrochloride with other drugs which follow the same route of biotransformation may result in
altered bioavailability of verapamil or these drugs. 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 verapamil hydrochloride to maintain optimum therapeutic blood levels.

Drugs known to be inhibitors of the cytochrome P450 system include: azole antifungals, cimetidine, cyclosporin, erythromycin, quinidine, terfenadine, warfarin.

Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, rifampin.

Drugs known to be biotransformed via P450 include: benzodiazepines, flecainide, imipramine, propafenone, theophylline.

**Alpha-adrenergic blockers:** Concomitant use of verapamil hydrochloride with alpha-adrenergic blockers may result in an exaggerated hypotensive response.

**Anti-neoplastic Agents:** Verapamil inhibits P-glycoprotein mediated transport of anti-neoplastic agents out of tumour cells, resulting in their decreased metabolic clearance. Dosage adjustment of anti-neoplastic agents should be considered when verapamil hydrochloride is administered concomitantly.

**Acetylsalicylic acid:** Potential adverse reactions in terms of bleeding due to synergistic antiplatelet effects of the two agents should be taken into consideration in patients taking acetylsalicylic acid and verapamil hydrochloride concomitantly.

**Carbamazepine:** Verapamil hydrochloride therapy may increase carbamazepine concentrations during combined therapy. This may produce carbamazepine side effects such as diplopia, headache, ataxia or dizziness.

**Cimetidine:** The interaction between cimetidine and chronically administered verapamil hydrochloride has not been studied. In acute studies of healthy volunteers clearance of verapamil was either reduced or unchanged.

**Concomitant Antiarrhythmic Therapy:** (see **WARNINGS**)

**Cyclosporin:** Verapamil hydrochloride therapy may increase serum levels of cyclosporin.

**Dantrolene:** Two animal studies suggest concomitant use of intravenous verapamil hydrochloride and intravenous dantrolene sodium may result in cardiovascular collapse. There has been one report of hyperkalemia and myocardial depression following the coadministration of oral verapamil hydrochloride and intravenous dantrolene.

**Inhalation Anesthetics:** Animal experiments have shown that inhalation anesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anesthetics and calcium antagonists, such as verapamil hydrochloride, should be titrated carefully to avoid excessive cardiovascular depression.

**Lithium:** Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant verapamil hydrochloride and lithium therapy with either no change or an increase in serum lithium levels. The addition of verapamil hydrochloride, however, has also resulted in the lowering of
serum lithium levels in patients receiving chronic stable oral lithium. Patients receiving both drugs must be monitored carefully.

Midazolam: Concomitant administration of midazolam and verapamil increased plasma levels of midazolam.

Neuromuscular Blocking Agents: Clinical data and animal studies suggest that verapamil hydrochloride may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of verapamil hydrochloride and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

Phenobarbital: Phenobarbital therapy may increase verapamil hydrochloride clearance.

Protein-bound Drugs: Because verapamil hydrochloride is highly protein bound, the drug should be used with caution in patients receiving any highly protein-bound drug such as anticoagulants, anticonvulsants and anti-inflammatory analgesics.

Rifampin: Therapy with rifampin may markedly reduce oral verapamil hydrochloride bioavailability.

### ADVERSE REACTIONS

The incidence of all adverse reactions, including those seen with both the oral and intravenous use of verapamil hydrochloride, is about 10.6%, with 6.7% associated with oral administration. Approximately 1.4% of these patients required discontinuation of the drug because of side effects. The most common adverse effect seen with oral verapamil hydrochloride is constipation, while hypotension and bradycardia are more common with its intravenous use.

In rare cases of hypersensitive patients, broncholaryngeal spasm accompanied by itch and urticaria have been reported.

Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty. One case of anaphylactic shock following intravenous verapamil hydrochloride has also been reported.

The following adverse reactions were reported with intravenous verapamil hydrochloride use in controlled clinical trials involving 324 patients.

**Cardiovascular**

Symptomatic hypotension (1.5%); bradycardia (1.2%); severe tachycardia (1.0%). The worldwide experience in open clinical trials in more than 7,900 patients was similar.

**Central nervous system**

Dizziness (1.2%); headache (1.2%). Although rare, cases of seizures during verapamil hydrochloride injection have been reported.
Gastrointestinal

Nausea (0.9%); abdominal discomfort (0.6%).

Respiratory

In rare cases of hypersensitive patients, broncholaryngeal spasm accompanied by itch and urticaria have been reported.

Miscellaneous

The following adverse reactions were reported in a few patients: Stevens-Johnson syndrome, erythema multiforme, skin reactions, exanthema, urticaria, pruritus, muscular cramps, arthralgia, emotional depression, vertigo, confusion, rotary nystagmus, diplopia, impaired vision, sleepiness, insomnia, muscle fatigue, diaphoresis, painful coldness and numbness in the extremities, paresthesia, hyperkinesia, impotence.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

The following symptoms have been identified: Hypotension varying from transient to severe, bradycardia up to high degree AV block and sinus arrest, hyperglycemia, stupor and metabolic acidosis. Conduction disturbances seen included prolongation of AV conduction time; AV dissociation; nodal rhythm; ventricular fibrillation and ventricular asystole.

Treatment

Treatment of overdosage should be supportive and individualized. Beta-adrenergic stimulation and/or parenteral administration of calcium solutions (calcium chloride or calcium gluconate) may increase calcium ion influx across the slow channel.

These pharmacologic interventions have been effectively used in treatment of deliberate overdosage with oral verapamil hydrochloride. Clinically significant hypertensive reactions should be treated with vasopressor agents. AV block should be treated with atropine and cardiac pacing.

Asystole should be handled by the usual measures including isoproterenol hydrochloride, other vasopressor agents, or cardiopulmonary resuscitation. See Table below for suggested treatment.

Verapamil hydrochloride cannot be removed by hemodialysis.
**Suggested treatment of Acute Cardiovascular Reactions***

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Proven Effective Treatment</th>
<th>Supportive Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hypotension requiring treatment</td>
<td>Calcium chloride (i.v.) Metaraminol bitartrate (i.v.) Dopamine HCl (i.v.) Isoproterenol HCl (i.v.) Norepinephrine bitartrate (i.v.)</td>
<td>I.V. fluids Trendelenburg position</td>
</tr>
<tr>
<td>2. Bradycardia, AV block, asystole</td>
<td>Calcium chloride (i.v.) Norepinephrine bitartrate (i.v.) Isoproterenol HCl (i.v.) Atropine sulfate (i.v.) Cardiac pacing</td>
<td>I.V. fluids (slow drip)</td>
</tr>
<tr>
<td>3. Rapid ventricular rate (due to antegrade conduction in flutter, fibrillation with W-P- W or L-G-L syndromes)</td>
<td>D.C. cardioversion (high energy may be required) Procainamide (i.v.) Lidocaine HCl (i.v.)</td>
<td>I.V. fluids (slow drip)</td>
</tr>
</tbody>
</table>

* Actual treatment and dosage should depend on the severity of the clinical situation, and the judgement of the attending physician

**DOSAGE AND ADMINISTRATION**

VERAPAMIL HYDROCHLORIDE INJECTION, USP SHOULD BE ADMINISTERED AS A SLOW INTRAVENOUS INJECTION OVER AT LEAST TWO MINUTE PERIOD OF TIME IN HOSPITAL, WHERE CORONARY CARE FACILITIES ARE AVAILABLE AND CONTINUOUS ELECTROCARDIOGRAPHIC AND BLOOD PRESSURE MONITORING ARE PERFORMED.

VERAPAMIL HYDROCHLORIDE INJECTION, USP should be inspected visually for particulate matter and discolouration prior to administration. Use only if solution is clear. Any unused portion should be discarded immediately.

Admixing verapamil hydrochloride with sodium lactate in polyvinyl chloride containers, albumin, amphotericin B, hydralazine HCl, and trimethoprim with sulfamethoxazole should be avoided. Verapamil hydrochloride will precipitate in any solution with a pH above 6.

The dosage of verapamil hydrochloride should be individualized for each patient based on response and tolerance. In some cases doses smaller than those recommended appear sufficient. Injection should only be continued to the point of therapeutic effect. Intravenous use of verapamil hydrochloride may be accompanied by a hypotensive response which can be precipitous, by a rapid ventricular rate, extreme bradycardia or asystole.
An intravenous preparation of calcium chloride or calcium gluconate should be available in the event of any adverse hemodynamic phenomenon. Concomitant use of beta-blockers is contraindicated.

The recommended doses of Verapamil Hydrochloride Injection, USP are as follows:

**Adult**

**Initial Dose**: 5 to 10 mg (0.075-0.15 mg/kg) may be given as an intravenous bolus over at least 2 minutes.

**Repeat Dose**: 10 mg (0.15 mg/kg) may be injected 30 minutes after the first dose, if the initial response is not adequate. An optimal interval for subsequent intravenous doses has not been determined and should be individualized for each patient.

**Elderly Patients**: The dose should be administered over at least three minutes to minimize the risk of untoward drug effects.

**Children**

**Initial Dose**

0 to 1 year: 0.1 to 0.2 mg/kg (usual single dose range 0.75 to 2 mg) should be administered as an intravenous bolus over at least 2 minutes under continuous ECG monitoring.

1 to 15 years: 0.1 to 0.3 mg/kg (usual single dose range 2 to 5 mg) should be administered as an intravenous bolus over at least 2 minutes. **Do not exceed 5 mg.**

**Repeat Dose**

0 to 1 year: 0.1 to 0.2 mg/kg (usual single dose range 0.75 to 2 mg) 30 minutes after the first dose if the initial response is not adequate, under continuous ECG monitoring. An optimal interval for subsequent doses has not been determined, and should be individualized for each patient.

1 to 15 years: 0.1 to 0.3 mg/kg (usual single dose range 2 to 5 mg) 30 minutes after the first dose if the initial response is not adequate. An optimal interval for subsequent doses has not been determined, and should be individualized for each patient. **Do not exceed 10 mg as a single dose.**

Oral therapy with verapamil hydrochloride should replace i.v. therapy as soon as possible, when the physician wishes to continue treatment with verapamil hydrochloride. Duration of treatment will depend on the underlying cause and history of recurrence.
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Verapamil Hydrochloride

Chemical Name: Benzeneacetonitrile,α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]-methylamino]propyl]-3,4-dimethoxy-α-(1-methylethyl) hydrochloride

Structural Formula:

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{CH}_3 & \quad \text{H}_2\text{CO} \\
\text{H}_3\text{CO} & \quad \text{CH}_3
\end{align*}
\]

Molecular Formula: \( C_{27}H_{38}N_2O_4 \cdot \text{HCl} \)

Molecular Weight: 491.07

Description:

Verapamil hydrochloride occurs as a white or almost white, crystalline powder, practically free of odor, with a bitter taste. It is soluble in water; freely soluble in chloroform; sparingly soluble in alcohol; practically insoluble in ether.

It has a pH between 4.5 and 6.5 and a melting range between 140° and 144°C.

Composition:

VERAPAMIL HYDROCHLORIDE INJECTION, USP is a sterile, nonpyrogenic solution containing verapamil hydrochloride 2.5 mg/mL (equivalent to 2.3 mg/mL verapamil) and sodium chloride 8.5 mg/mL in water for injection. The solution contains no bacteriostat or antimicrobial agent and is intended for single use only. May contain hydrochloric acid for pH adjustment; pH 4.9 (4.0 to 6.5).

Stability and Storage Recommendations:

Store between 15° and 25°C. Protect from light and freezing. Retain in carton until ready for use. For single use only. Discard unused portion.
AVAILABILITY OF DOSAGE FORMS

VERAPAMIL HYDROCHLORIDE INJECTION, USP is supplied in single dose containers as follows:

- 2.5 mg/mL in 2 and 4 mL (5 mg/2 mL, 10 mg/4 mL) ampoules, sleeves of 10, List 4011.
- 2.5 mg/mL in 2 and 4 mL (5 mg/2 mL, 10 mg/4 mL) fliptop vials, cartons of 5, List 1144.

PHARMACOLOGY

Animal Pharmacology

In Vitro

Verapamil has been reported to impede the transmembrane slow inward movement of Ca++ during the plateau phase of the intracellular action potential recorded from isolated Purkinje fibers. It also prolongs the action potential duration, prolonging the refractory period, without affecting the resting membrane potential, upstroke velocity of Phase 0, overshoot or membrane responsiveness.

Other reported studies, using cardiac preparations from several species, showed that verapamil reduced atrial or ventricular myocardial contractility (negative inotropic effect) in the same concentration range required to suppress SA or AV nodal pacemaker activity.

Effects of verapamil on myocardial contractility, automaticity or action potential configuration are reversed by isoproterenol or calcium.

In Vivo

In dogs, mice, rats, rabbits, pigs and cats, verapamil has been reported to have an antiarrhythmic activity; it protects against arrhythmias induced by agents such as acetylcholine, aconitine, amitryptiline, cardiac glycosides or catecholamines, or by coronary artery ligation.

The protective effect of verapamil on the ventricular rate (i.e. slowing) during either atrial flutter or fibrillation is the result of a decrease in the number of atrial impulses conducted to the ventricles because of a slowing of AV nodal conduction.

Electrocardiographic effects of verapamil are primarily limited to prolongation of the PR interval.

In the dog, oral sublingual and intravenous verapamil decreases coronary arterial resistance and increases coronary blood flow even in the presence of a reduced systemic arterial blood pressure.

Other hemodynamic effects of verapamil in dogs include a slight reduction of arterial blood pressure associated with a small reflex increase in heart rate, and a slight increase or no change in cardiac output, stroke volume, and left ventricular maximum dp/dt. Verapamil also decreases blood pressure when given i.v. to anesthetized normotensive rats.
TOXICOLOGY

Acute Toxicity

The acute toxicity of verapamil administered by a variety of routes, was studied in mice, rats, guinea pigs and dogs.

**Acute LD₅₀ Values of Verapamil**

<table>
<thead>
<tr>
<th>Species</th>
<th>Route</th>
<th>LD₅₀ (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice</td>
<td>p.o.</td>
<td>163</td>
</tr>
<tr>
<td></td>
<td>s.c.</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>i.p.</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>8</td>
</tr>
<tr>
<td>Rat</td>
<td>p.o.</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td>s.c.</td>
<td>107</td>
</tr>
<tr>
<td></td>
<td>i.p.</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>i.m.</td>
<td>118</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>16</td>
</tr>
<tr>
<td>Guinea Pig</td>
<td>p.o.</td>
<td>140</td>
</tr>
<tr>
<td>Dog</td>
<td>i.m.</td>
<td>25</td>
</tr>
</tbody>
</table>

Signs of toxicity included tachypnea, prostration, tremors, and tonic spasms/convulsions followed by death.

Subacute Toxicity

Rats

Rats were dosed daily with intravenous verapamil for four weeks at 0.2, 1.0 or 5.0 mg/kg/day. 1.0 mg/kg dose produced a slight decrease in body weight gain during the first week of treatment. A higher dose of 5.0 mg/kg, in addition to an initial weight loss, produced a period of tachypnea and prostration starting immediately after administration and lasting 15 minutes.

Dogs

Dogs were dosed with intravenous verapamil at 0.1, 0.4 or 1.6 mg/kg/day for four weeks. Restlessness, salivation, forced respiration and pronounced sensitivity to sound were observed at 1.6 mg/kg dose.

Verapamil, at doses of 62.5 mg/kg/day or greater, administered for longer than 2 to 3 months, has been reported to cause cataract in 8 out of 35 beagle dogs. Other lens changes, usually involving the suture lines, were reported at 30 mg/kg/day and above in most of the remaining dogs. It appears that the cataractogenic activity of verapamil is specific for the beagle dog.
Reproduction and Teratology

Reproduction studies in rabbits at oral doses of up to 15 mg/kg/day showed that verapamil had no effect on
the dams or litter size, number of live or dead fetuses, number of resorptions nor was the drug teratogenic.

In rats, fractionated daily oral doses of up to 60 mg/kg/day administered during the period of organogenesis
were not teratogenic. However, the high dose reduced the number of live fetuses and increased the number
of late resorptions. This dose also retarded fetal development.

Oral Verapamil had no teratogenic or antifertility effect in female Wistar rats receiving up to 55 mg/kg/day
in the diet or 100 mg/kg/day by gavage or in rabbits receiving up to 15 mg/kg/day in the diet. In the rat,
doses of 25 and 100 mg/kg/day did delay embryologic development and increased the number of
resorptions.

In a multi-mating study, dietary verapamil was administered to both female and male rats at 25 mg/kg/day
for 70 days prior to mating and through two consecutive matings. A significant reduction in the number of
live pups and a slight reduction in the number of litters were observed. When the dose was reduced to
12.5 mg/kg/day for the third mating, no evidence of teratogenicity or embryotoxicity were observed.

Mutagenicity

Verapamil was not mutagenic when incubated with five (5) histidine - requiring mutants of Salmonella
typhimurium (Ames Test) at up to 3 mg/plate, either alone or in the presence of a rat liver microsomal
fraction.
REFERENCES


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