VERAPAMIL

THERAPEUTICS

Brands
- Calan, Cordilo, Securon, Verapress, Vertab, Univer, Covera-HS, Verelan, Isoptin SR

Generic?
Yes

Class
- Antihypertensive, calcium channel blocker

Commonly Prescribed for
(FDA approved in bold)
- Angina (vasospastic or effort associated)
- Essential hypertension
- Paroxysmal supraventricular tachycardia, atrial fibrillation/flutter (IV formulation)
- Migraine prophylaxis
- Cluster headache prophylaxis
- Peyronie’s disease, plantar fibromatosis, Dupuytren’s disease (gel)

How the Drug Works
- Migraine/cluster: Proposed prior mechanisms included inhibition of smooth muscle contraction preventing arterial spasm and hypoxia, prevention of vasoconstriction or platelet aggregation, and alterations of serotonin release and uptake. Prevention of cortical spreading depression may be the mechanism of action for all migraine preventives
- Voltage-gated L-calcium channels mediate calcium influx and are important in regulating neurotransmitter and hormone release

How Long Until It Works
- Migraines – may decrease in as little as 2 weeks, but can take up to 3 months on a stable dose to see full effect
- Cluster – usually effective in weeks

If It Works
- Migraine – goal is a 50% or greater reduction in migraine frequency or severity. Consider tapering or stopping if headaches remit for more than 6 months or if considering pregnancy
- Cluster – reduction in the severity or frequency of attacks

If It Doesn’t Work
- Increase to highest tolerated dose

- Migraine/cluster: address other issues, such as medication-overuse, other coexisting medical disorders, such as anxiety, and consider changing to another agent or adding a second agent

Best Augmenting Combos for Partial Response or Treatment-Resistance
- Migraine: For some patients with migraine, low-dose polytherapy with 2 or more drugs may be better tolerated and more effective than high-dose monotherapy. May use in combination with AEDs, antidepressants, natural products, and non-medication treatments, such as biofeedback, to improve headache control
- Cluster: At the start of the cycle can use a steroid slam and taper. Valproic acid, lithium, topiramate, and methysergide are effective for many cluster patients

Tests
- At higher doses, monitor ECG for PR interval

ADVERSE EFFECTS (AEs)

How Drug Causes AEs
- Direct effects of calcium receptor antagonism, slowing of AV conduction

Notable AEs
- Bradycardia, hypotension, weakness, headache
- Constipation, nausea, myalgia
- Allergic rhinitis, ankle edema, gingival hyperplasia
- First degree AV block
- Upper respiratory infection, flu-like syndrome

- Pulmonary edema, worsening of CHF in patients with moderate to severe cardiac function
- Rarely produces second or third degree AV block
- Rare hypertrophic cardiomyopathy
- Can worsen muscle transmission and cause weakness in patients with muscular dystrophies
VERAPAMIL

Weight Gain
- Unusual

Sedation
- Unusual

What to Do About AEs
- For common AEs, lower dose, change to extended-release formulation, or switch to another agent. For serious AEs, do not use

Best Augmenting Agents for AEs
- Constipation can be treated by usual agents, such as magnesium

DOSING AND USE

Usual Dosage Range
- 120–480 mg/day

Dosage Forms
- Tablets: 40, 80, 120 mg. Extended release 120, 180, 240 mg
- Extended-release capsules: 100, 180, 240, 300, 360 mg
- Injection: 2.5 mg/mL
- Gel: 15% transdermal

How to Dose
- Migraine: Initial dose 40–120 mg/day and effective usually at 120–360 mg/day for most patients. Gradually increase over days to weeks to usual effective dose. Immediate release dose TID. Sustained or extended release BID or once daily
- Cluster: Start at 120–240 mg daily and increase by 40–120 mg/week until attacks are suppressed or a daily dose of 960 mg/day. May use as much as 1200 mg/day with ECG monitoring

Dosing Tips
- Doses above 360 mg had no additional antihypertensive effect in clinical trials
- Can titrate with immediate release then change to longer acting once at a stable dose

Overdose
- Bradycardia, hypotension, with the possibility of low-output heart failure and shock. Treat with lavage, charcoal, cathartics. For hypotension, use dopamine, IV calcium, beta-agonists, or norepinephrine. For AV block, atropine is also helpful. For rapid ventricular rate due to anterograde conduction, use D.C. cardioversion or IV lidocaine

Long-Term Use
- Safe for long-term use

Habit Forming
- No

How to Stop
- Decrease 2 weeks after cessation of cluster attacks. Less risk of rebound tachycardia than beta-blockers

Pharmacokinetics
- Metabolized by CYP450 system, especially CYP3A4. Half-life 2.8–7.4 h with 1 dose but increased with repetitive dosing. SR about 12 h. Tmax 1–2 h, 11 h extended release, 7–9 h sustained release. Oral bioavailability 20–35%, 90% protein binding

Drug Interactions
- Verapamil can alter hepatic function, increasing plasma concentrations and effect of anesthetics, digoxin, statins, ethanol, buspirone, imipramine, prazosin, sirolimus, tacrolimus, carbamazepine, theophyllines, some benzodiazepines, and muscle relaxants
- Verapamil can lower lithium levels but increase toxicity
- Phenytin, rifampin, and calcium salts decrease concentration of verapamil
- Potent CYP3A4 inhibitors such as ketoconazole increase levels
- H2 antagonists (cimetidine, ranitidine) increase verapamil levels
- Use with beta-blockers can be synergistic or additive, use with caution

Other Warnings/Precautions
- Increased intracranial pressure with verapamil IV in patients with supratentorial tumors
- Elevated liver enzymes have occurred
VERAPAMIL (continued)

Do Not Use
- Sick sinus syndrome, greater than 1st degree heart block
- Severe CHF, cardiogenic shock, severe left ventricular dysfunction
- Hypotension less than 90 mm Hg systolic
- Proven hypersensitivity to verapamil or other calcium channel blockers
- Do not give IV verapamil in close proximity to IV beta-blockers

Pregnancy
- Category C (all calcium channel blockers). Use only if potential benefit outweighs risk to the fetus

Breast Feeding
- Not recommended. Verapamil is found in breast milk

SPECIAL POPULATIONS

Renal Impairment
- About 70% of verapamil metabolites are secreted by the kidney. Monitor for PR interval prolongation and side effects. Use with caution

Hepatic Impairment
- Verapamil is highly metabolized by the liver. Give about 30% of usual dose to patients with severe dysfunction

Cardiac Impairment
- Do not use in acute shock, severe CHF, hypotension, and greater than 1st degree heart block as above

Elderly
- Use with caution and start with lower doses

Children and Adolescents
- Little is known about efficacy or safety. Use with caution if at all

THE ART OF NEUROPHARMACOLOGY

Potential Advantages
- Proven effectiveness in cluster headache and better tolerated than most other preventive options, but may need a very high dose

Potential Disadvantages
- Not a first-line agent in migraine (limited evidence of efficacy). Multiple potential drug interactions

Primary Target Symptoms
- Headache frequency and severity

Pearls
- Relatively little evidence for effectiveness in migraine, but first-line agent for cluster headache
- For patients with cycles of cluster headache, taper off starting 2 weeks after last attack
- May help patients with migraine with atypical or prolonged aura (i.e., hemiplegic migraine)
There is no evidence that verapamil is more effective in the treatment of hypertension beyond 360 mg/day
Suggested Reading


