guanFACINE

Pharmacology, Warnings, Pregnancy, Lactation, Side Effects, IV Compatibility, Dosage, Additional Dosage

Pharmacology (Top)

Pharmacology

Guanfacine is a centrally-acting alpha-2-adrenergic receptor agonist.

By stimulating the brainstem, guanfacine decreases sympathetic tone to the heart and blood vessels, resulting in decreased heart rate and peripheral vascular resistance.

Guanfacine is approved by the FDA for the treatment of hypertension, alone or in combination with other antihypertensive agents, especially thiazide diuretics. It is also designated as an orphan drug for the treatment of Fragile X syndrome. The extended-release formulation is approved by the FDA for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Guanfacine has been used for the treatment of heroin withdrawal symptoms and hypertension in pregnancy; however, this use is not approved by the FDA.

Pharmacokinetics

The mean bioavailability of guanfacine ranges from 81% to 100% in patients with normal renal and hepatic function. There is no significant first-pass metabolism.

Peak plasma concentrations (Cmax) for guanfacine immediate-release occur from 1 to 4 hours (Tmax) with an average of 2.6 hours after single oral doses or at steady state. The area under the concentration-time curve (AUC) increases linearly with the dose. The antihypertensive effect has a duration of 24 hours in patients with normal renal and hepatic function. A comparison study suggests that the Cmax is 60% lower and AUC is 43% lower, respectively, for guanfacine extended-release compared to guanfacine immediate-release. Therefore, the relative bioavailability of guanfacine extended-release to guanfacine immediate-release is 58%. The pharmacokinetic profile was affected by intake of food when a single dose of 4 mg guanfacine extended-release was administered with a high fat breakfast. The mean exposure increased (Cmax about 75% and AUC about 40%) compared to dosing in a fasted state.

The average plasma protein binding ranges from 64% to 72% in patients with normal renal and hepatic function. There is also extensive uptake of this drug into erythrocytes.

The volume of distribution (Varea) averages 6.3 L/kg in patients with normal renal and hepatic function. The volume of distribution (Varea) is unchanged in patients with severe renal dysfunction.

The plasma clearance averages 5.9 mL/min/kg in patients with normal renal and hepatic function. Plasma clearance is unchanged in patients with severe renal dysfunction. While renal clearance is significantly decreased in patients with renal dysfunction, total body clearance is maintained due to increased liver metabolism in these patients.

The elimination half-life averages 13.4 hours in patients with normal renal and hepatic function. Half-life is unchanged in patients with severe renal dysfunction.

Guanfacine is primarily eliminated by the kidney. The percentage of a dose that is excreted as unchanged drug

in the urine averages 50% in patients with normal renal function. The plasma clearance to creatinine clearance ratio of guanfacine is greater than one, indicating active tubular secretion. guanfacine also undergoes metabolism primarily by CYP450 3A4 to at least 4 inactive metabolites. Neither the parent drug nor its metabolites accumulate after chronic dosing in patients with severe renal dysfunction due to increased hepatic metabolism in these patients. Progressively less unchanged drug is excreted in the urine with decreasing degrees of renal function. The fraction of unchanged drug excreted in the urine of patients with an average creatinine clearance of 10 mL/min averages 8%, compared with 57% in patients with normal renal function.

There are no data on the pharmacokinetic disposition of guanfacine in patients with liver dysfunction.

Limited data suggest that guanfacine is not removed by hemodialysis. There are no data on the peritoneal dialysis clearance of guanfacine.

Warnings (Top)

(Severity: General Warning Exists)

As with other antihypertensives, guanfacine should be used with caution in patients with recent myocardial infarction, cerebrovascular disease, or in those with severe coronary insufficiency.

Guanfacine should be used with caution in patients with a history of hypotension, heart block, bradycardia, or cardiovascular disease, because it can decrease blood pressure and heart rate. Caution should be used in treating patients who have a history of syncope or may have a condition that predisposes them to syncope, such as hypotension, orthostatic hypotension, bradycardia, or dehydration.

As with all centrally-acting alpha-2-adrenergic receptor agonists, patients should be warned of sedative effects when initiating therapy. These effects are generally dose related.

Patients should be advised against abrupt cessation of alpha-2-adrenergic agonist therapy as it can lead to increases in plasma and urinary catecholamines, symptoms of anxiety and nervousness, and in some cases increases in blood pressure.

The frequency of rebound hypertension is low, but it can occur. When rebound occurs, it does so after 2 to 4 days. In most cases, after abrupt withdrawal of guanfacine, blood pressure returns to pretreatment levels slowly (within 2 to 4 days) without ill effects.

Patients should be advised to avoid becoming dehydrated or overheated while on guanfacine therapy.

Pregnancy (Top)

(Severity: Minor Female Pregnancy Warning)

Guanfacine has been assigned to pregnancy category B by the FDA. Animal studies have revealed evidence of maternal toxicity and decreased fetal survival after doses 100 and 200 times the maximum recommended human dose (on a per kg basis) were given to rabbits and rats, respectively. Doses less than these were not associated with any evidence of harm to the fetus. There are no controlled data in human pregnancy. Guanfacine should only be given during pregnancy when need has been clearly established.

Guanfacine effectively reduced blood pressure in 30 pregnant women with preeclampsia, but edema and proteinuria persisted. There were no notable changes in either the fetal or maternal heart rate. Of the 30

neonates, six were considered "small for date babies", but this was expected given the underlying diseases of the mothers. No congenital anomalies were observed among the offspring, and all developed normally.

Lactation (Top)

(Severity: No Lactation Literature Available)

There are no data on the excretion of guanfacine into human milk. Studies have shown that guanfacine is excreted into the milk of lactating rats. The manufacturer recommends that due to the potential for serious adverse reactions in nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Side Effects (Top)

General

Guanfacine is generally well-tolerated. In a study of 580 hypertensive patients, only 7% withdrew due to adverse side effects. In addition, most side effects were mild, dose-related, and resolved over time.

Nervous system

Nervous system side effects have included fatigue or a sedative effect and dizziness in 33% and 15% of patients, respectively. After one year of therapy, the incidence of these side effects falls to 6% and 1%, respectively. Headaches occur in less than 5% of patients. Nervous system side effects associated with the extended-release formulation have included somnolence (38%), fatigue (14%), headache (24%), lethargy (6%), dizziness (6%), and postural dizziness (less than 2%).

Gastrointestinal

Gastrointestinal side effects have included dry mouth in up to 60% of patients. Constipation has been associated with the use of this drug in 14% of patients. After one year of therapy the incidence of dry mouth and constipation averages 15% and 3%, respectively. Gastrointestinal side effects associated with the extended-release formulation have included dry mouth (4%), upper abdominal pain (10%), nausea (6%), and dyspepsia (less than 2%).

Cardiovascular

Cardiovascular side effects have included orthostatic hypotension and palpitations, each of which is rare. There is limited, indirect (ECG) evidence of left ventricular hypertrophy resolution after guanfacine therapy. Cardiovascular side effects associated with the extended-release formulation have included hypotension/decreased blood pressure (6%), atrioventricular block (less than 2%), bradycardia (less than 2%), and sinus arrhythmia (less than 2%) .

Genitourinary

Genitourinary complaints in male patients are limited to impotence, which is associated with higher doses (daily doses of 3 mg or more).

Metabolic

Metabolic side effects associated with the extended-release formulation have included decreased appetite (5%), and constipation (3%).

Psychiatric

Psychiatric side effects associated with the extended-release formulation have included irritability (6%)

Respiratory

Respiratory side effects associated with the extended-release formulation have included asthma (less than 2%).

IV Compatibility

Dosage (Top)

Usual Adult Dose

Hypertension

Initial dose: 1 mg orally once a day at bedtime, when given alone or in combination with another antihypertensive drug.
Maintenance dose: 1 to 3 mg orally once a day at bedtime.

Usual Pediatric Dose

Attention Deficit Disorder

Only the guanfacine extended-release formulation is indicated for ADHD.

Children 6 to 17 years of age:

Initial dose: 1 mg extended-release orally once a day in the morning

Dosage should be adjusted in increments of no more than 1 mg/week.

Maintenance dose: 1 to 4 mg extended-release orally once daily in the morning, depending on clinical response and tolerability.

Additional Dosage (Top)

Renal Dose Adjustments

When prescribing for patients with renal impairment, the low end of the dosing range should be used.

Liver Dose Adjustments

Data not available

Dose Adjustments

If after 3 to 4 weeks of guanfacine immediate-release therapy the 1 mg does not give a satisfactory result, a dose of 2 mg may be given. Most of the effect of guanfacine is seen at 1 mg. Higher daily doses have been used, but adverse reactions increase significantly with doses above 3 mg/day.

Precautions

Guanfacine extended-release should not be substituted for guanfacine immediate-release on a mg to mg basis, because of differing pharmacokinetic profiles.

Guanfacine extended-release should be dosed once daily, and should not be crushed, chewed or broken before swallowing because this will increase the rate of guanfacine release. It should not be administered with high fat meals, due to increased exposure.

The effectiveness of guanfacine extended-release for longer-term use (more than 9 weeks) has not evaluated in controlled trials. Health care providers electing to use guanfacine extended-release for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

If patients are switched from the immediate-release to the extended-release formulation, the immediate-release should be discontinued and the extended- release titrated according to manufacturer guidelines.

Guanfacine extended-release has not been studied for doses over 4 mg per day.

Safety and effectiveness have not been established in pediatric patients less than 6 years of age.

Dialysis

Patients on dialysis can be given usual doses of guanfacine hydrochloride as the drug is poorly dialyzed.

Other Comments

Infrequent, transient elevations in blood pressure above original baseline (i.e., rebound) have been reported to occur upon abrupt discontinuation of guanfacine. To minimize these effects, the dose should generally be tapered in decrements of no more than 1 mg every 3 to 7 days.