cloNIDine

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

Pharmacology (Top)

Pharmacology

Clonidine is a central postsynaptic alpha-2-adrenergic receptor agonist.

Clonidine lowers blood pressure by stimulating central postsynaptic alpha-2-adrenergic receptors, thus inhibiting sympathetic neurotransmission. The net result is a decrease in vasomotor tone and heart rate. Clonidine also produces analgesia when administered epidurally by preventing pain signal transmission to the brain at presynaptic and postjunctional alpha-2-adrenoreceptors in the spinal cord.

Clonidine is approved by the FDA for the treatment of hypertension alone or with other antihypertensive drugs. Epidural clonidine is approved in combination with opioids for the treatment of severe pain in cancer patients. Clonidine extended-release tablets are approved by the FDA for the treatment of attention deficit hyperactivity disorder (ADHD) as monotherapy or as adjunctive therapy to stimulant medications. Clonidine extended-release tablets and oral suspension are approved by the FDA for treatment of hypertension.

While not FDA approved indications, other potential uses of clonidine have included analgesia and anesthesia potentiation (i.e., intrathecal), anxiety, atrial fibrillation, attention deficit disorder, bipolar disorder, chronic stable angina, congestive heart failure, diminishes hyperadrenergic response to carotid endarterectomy, diagnosis of depression, diagnosis of pheochromocytoma, diarrhea, dysmenorrhea, growth hormone stimulation test, malignant hypertension, menopausal vasomotor symptoms (hot flashes), migraine prophylaxis, neurogenic bladder, neuroleptic-induced akathisia, obstructive sleep apnea, opiate withdrawal symptoms, panic disorder, paroxysmal hyperhidrosis, perioperative myocardial ischemia, portal hypertension, posttraumatic stress disorder, premenstrual syndrome, preoperative sedation and anxiolysis, prevention of cyclosporine-induced nephrotoxicity, prevention of postoperative nausea and vomiting, proctalgia fugax, Raynaud's disease, reduction of anesthetic requirements, reflex sympathetic dystrophy, restless leg syndrome, sialorrhea, smoking cessation, social phobia, tardive dyskinesia, Tourette's syndrome, and transmural and/or lateral wall myocardial infarction. Epidural clonidine has been used for obstetrical, postpartum, and perioperative pain management and as an alternative to epidural opioids. Injectable clonidine has been investigated for its potential ability to treat postoperative shivering. In clinical studies, orally administered clonidine has been successfully used in conjunction with oral diluted tincture of opium in infants with intrauterine exposure to methadone or heroin who experienced neonatal abstinence syndrome (NAS). The median length of therapy (11 days) in infants being treated with this combination was 27% shorter than in infants being treated with tincture of opium alone (15 days).

Pharmacokinetics

Clonidine is available for oral administration, for transdermal delivery, and for epidural infusion. The average bioavailability of clonidine tablets ranges from 75% to 95%. After oral administration, peak plasma concentrations are reached within 3 to 5 hours (Tmax). The average bioavailability of clonidine patches ranges from 48% to 51%. Therapeutic plasma concentrations are reached within 2 to 3 days after application of clonidine patches. The time to peak CSF levels for epidurally administered clonidine averaged 26 minutes. A comparison across studies suggests that the Cmax is 50% lower for extended-release clonidine compared to immediate-release clonidine. After administration of extended-release clonidine, maximum clonidine concentrations were approximately 50% of the immediate-release clonidine maximum concentrations and occurred approximately 5 hours later relative to immediate-release clonidine. Similar elimination half-lives were

observed and total systemic bioavailability following extended-release clonidine was approximately 89% of that following Catapres.

The average plasma protein binding ranges from 20% to 40%.

The volume of distribution averages 2.1 L/kg in patients with normal renal and hepatic function.

The average plasma clearance ranges from 2.6 to 4.0 mL/min/kg in patients with normal renal and hepatic function.

The average elimination half-life ranges from 8 to 15 hours. One study reported a half-life as long as 20 hours in patients with normal renal and hepatic function. The average CSF elimination half-life of epidurally administered clonidine ranges from 0.8 to 1.8 hours. The elimination half-life is significantly increased in patients with end-stage renal disease and averages 40 hours.

Clonidine is primarily eliminated by the kidney. Forty-two percent to 77% of an administered dose is excreted unchanged in the urine. A minor percentage of a dose is metabolized, primarily to p-hydroxyclonidine. Some data suggest enterohepatic recycling of clonidine.

Clonidine is not significantly removed by hemodialysis. Its hemodialysis clearance averages 48 mL/min. Less than 5% of a dose is removed after a 4-hour dialysis session. (Removal of clonidine by hemodialysis with hemoperfusion has been demonstrated.) There are no data on the peritoneal dialysis clearance of clonidine.

Warnings (Top)

(Severity: General Warning Exists)

Epidural administration is contraindicated in patients receiving anticoagulant therapy, patients with bleeding diathesis, and in the presence of an injection site infection.

Epidural clonidine is not recommended for obstetrical, postpartum, or perioperative pain management. The risk of hypotension and bradycardia may not be acceptable in these patients. However, in specific obstetrical patients, the benefit may outweigh the risk. In addition, epidural clonidine is not recommended in patients with severe cardiovascular disease or hemodynamic instability. Clonidine decreases sympathetic outflow from the central nervous system resulting in decreases in peripheral resistance, renal vascular resistance, heart rate, and blood pressure. Vital signs should be monitored frequently, especially in the first few days of therapy.

Patients should be instructed not to discontinue therapy without consulting their physician. Sudden cessation of clonidine can result in symptoms such as nervousness, agitation, headache, and confusion accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma. The likelihood of such reactions to discontinuation of clonidine therapy appears to be greater after administration of higher doses or continuation of concomitant beta-blocker treatment and special caution is therefore advised in these situations. Rare instances of hypertensive encephalopathy, cerebrovascular accidents and death have been reported after clonidine withdrawal. When discontinuing therapy with clonidine, the physician should reduce the dose gradually over 2 to 4 days to avoid withdrawal symptoms. An excessive rise in blood pressure following discontinuation of clonidine transdermal therapy can be reversed by administration of oral clonidine or by intravenous phentolamine. If therapy is to be discontinued in patients receiving a beta-blocker and clonidine concurrently, the beta-blocker should be withdrawn several days before the gradual discontinuation of clonidine transdermal therapy.

The sympatholytic action of clonidine may worsen sinus node dysfunction and atrioventricular (AV) block, especially in patients taking other sympatholytic drugs. There are postmarketing reports of patients with

conduction abnormalities and/or taking other sympatholytic drugs who developed severe bradycardia requiring IV atropine, IV isoproterenol and temporary cardiac pacing while taking clonidine.

Most patients who experience hypotension do so within the first four days of therapy; however, hypotension may occur throughout the duration of clonidine administration. Hypotension may occur more commonly in women, those receiving higher dosages, those weighing less, and in patients with severe cardiovascular disease or in those who are otherwise hemodynamically unstable. Hypotension usually responds to intravenous fluids, and if necessary, appropriate parenterally administered pressor agents such as ephedrine.

Clonidine should be used with caution in patients with severe coronary insufficiency, conduction disturbances, recent myocardial infarction, cerebrovascular disease, or chronic renal failure. In rare instances, loss of blood pressure control has been reported in patients using clonidine as instructed.

Patients who develop an allergic reaction to the transdermal therapy may also elicit an allergic reaction from the oral formulation is substituted (i.e., generalized rash, urticaria, or angioedema).

Clonidine transdermal therapy should not be interrupted during the surgical period. Blood pressure should be carefully monitored during surgery and additional measures to control blood pressure should be available if required. When considering initiation of clonidine transdermal during the perioperative period, it should be noted that therapeutic plasma clonidine levels are not achieved until 2 to 3 days after initial application of the clonidine transdermal system. Administration of the oral formulation should be continued to within four hours of surgery and resumed as soon as possible thereafter. The blood pressure should be carefully monitored and appropriate measures instituted to control it as necessary.

Several patients wearing an aluminized transdermal system have reported skin burns at the patch site while undergoing a magnetic resonance imaging scan (MRI). Because the clonidine patch contains aluminum, it is recommended to remove the system before undergoing an MRI.

Because of the potential to cause orthostatic hypotension and CNS adverse effects, clonidine meets the Beers criteria as a medication that is potentially inappropriate for use in older adults.

Patients who wear contact lenses should be cautioned that treatment with clonidine may cause dryness of the eyes.

Heart rate should be monitored in patients receiving clonidine concomitantly with agents known to affect sinus node function of AV nodal conduction (e.g., digitalis, calcium channel blockers, and beta-blockers). Sinus bradycardia resulting in hospitalization and pacemaker insertion has been reported in association with the use of clonidine concomitantly with diltiazem or verapamil.

Somnolence and sedation were commonly reported adverse reactions in clinical studies in patients taking clonidine extended-release tablets. Before using clonidine extended-release tablets with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), healthcare providers should consider the potential for additive sedative effects. Patients should be cautioned against operating heavy equipment or driving until they know how they respond to treatment. Patients should be advised to avoid use with alcohol.

If a patient is receiving clonidine and also taking tricyclic antidepressants the hypotensive effects of clonidine may be reduced.

Based on observations in patients in a state of alcoholic delirium, it has been suggested that high intravenous doses of clonidine may increase the arrhythmogenic potential (QT-prolongation, ventricular fibrillation) of high intravenous doses of haloperidol. The causal relationship and relevance for clonidine oral tablets have not been established.

Pregnancy (Top)

(Severity: Major Female Pregnancy Warning)

Clonidine has been assigned to pregnancy category C by the FDA. Animal studies have failed to reveal evidence of teratogenicity although an increased incidence of fetal resorption has been demonstrated in some species. While there are no controlled data from human pregnancy studies, clonidine has been used safely during all three trimesters of human pregnancy (1st trimester exposure has been limited). Clonidine should only be given during pregnancy when benefit outweighs risk.

Clonidine crosses the placenta. Limited data from 10 pregnant women have shown that the average umbilical cord to maternal clonidine concentration ratio averages 0.9. No adverse fetal effects in human pregnancy have been observed, but data are limited.

Data from the Michigan Medicaid Birth Defects Study (MMBDS) has revealed an unexpectedly high incidence of birth defects associated with the use of clonidine (written communication, Franz Rosa, MD, Food and Drug Administration, 1994). The MMBDS is a retrospective study of 229,101 pregnancies from 1985 to 1992, of which 59 were exposed to clonidine during the first trimester of pregnancy. Of the 59 pregnancies that were exposed to clonidine, there were 3 total and 2 cardiovascular defects observed (2.0 and 0.5 were expected, respectively). Cleft palate, spina bifida, polydactyly, limb reduction/syndactyly, or hypospadia were not observed. Because of the low numbers of exposures, no definite conclusions regarding an association or lack of association between clonidine and birth defects may be made.

Lactation (Top)

(Severity: Major Lactation Warning)

Clonidine is secreted into human milk. Limited data have failed to reveal evidence of adverse effects among nursing infants even though milk concentrations have shown to be double the concentration of clonidine compared with maternal serum concentrations. The manufacturer recommends that caution be used when administering clonidine to nursing women.

Limited data have shown that the average concentration of clonidine in human milk is approximately twice that observed in the maternal plasma. In one case, in which the mother was taking clonidine 37.5 mcg twice a day, the milk and maternal plasma clonidine levels were 0.60 and 0.33 ng per mL, respectively, while the plasma level in the infant was undetectable. No adverse effects were observed in the nursing infant. The authors calculated that, if the nursing infant consumed 150 mL per kg, it would have ingested clonidine 90 ng per kg per day, compared to the maternal drug dosage of 1,320 ng per kg per day (maternal weight 57 kg). Therefore, the relative clonidine dosage of the infant would have been 6.8% of the mothers. Two other reports of the use of clonidine during breast-feeding have shown that the plasma clonidine levels of the infants averaged 60% to 80% of the maternal plasma levels.

Prenatal exposure to clonidine has been associated with transitory hypertension during the first three days of life and with hyperactivity and sleep disturbances in six-year-old children. While hypotension has not been observed in nursing infants whose mothers were taking up to 0.4 mg of clonidine per day, data from long-term exposure to nursing infants are unavailable.

Side Effects (Top)

Other 1

The most common adverse side effects are related to the alpha-adrenergic blocking effects of clonidine. These side effects are dose-related, typically decrease over time, and mostly affect the nervous system, cardiovascular system, and the gastrointestinal system.

Nervous system

Nervous system side effects have included drowsiness (28%), dizziness (9%), somnolence (19%), fatigue (13%), headache (19%), irritability (6%), insomnia (6%), nightmares (3%), body temperature increased (1%), abnormal sleep-related event (1%), and tremor (3%). Patients with decreased autoregulation of cerebral blood flow appear to be at increased risk for clonidine-induced cerebral hypoperfusion if blood pressure is lowered too much or too quickly. This may be important in some elderly patients. Confusion (13.2%) and hallucinations (5.3%) have been reported with epidural usage. Dose-dependent sedative effects, memory impairment, and reduced cognitive performance have been reported in subjects receiving intravenous clonidine.

Cardiovascular

Cardiovascular side effects have included hypotension and sinus and atrioventricular arrhythmias. Postural hypotension occurs in 2% of patients. Rebound hypertension (which may be worse than pretreatment values) can present as irritability, tremors, headache, increased salivation, and palpitations. Rebound hypertension may be minimized by gradual reduction of dosage over two to four days.

Hypotension with epidural clonidine has been reported in 45% of 38 patients in one study. Hypotension occurred more commonly in the first four days, in women, in lower weight patients, and those receiving higher dosages.

Other cardiovascular side effects have included sinus bradycardia in approximately 0.3% of patients. A rare case of sinus arrest associated with clonidine has been reported. Patients with preexisting sinus node dysfunction, patients who have developed bradycardia while taking other sympatholytic agents, patients who are on another sympatholytic agent, and patients with renal dysfunction are at increased risk of clonidine-associated sinus bradycardia. Clonidine may cause hypertension in some patients with idiopathic orthostatic hypotension, particularly those with autonomic nervous system dysfunction. There have also been reports of congestive heart failure, electrocardiographic abnormalities (i.e., sinus node arrest, junctional bradycardia, high degree AV block, and arrhythmias), palpitations, Raynaud's phenomenon, syncope, and tachycardia. Cases of sinus bradycardia and atrioventricular block have been reported, both with and without the use of concomitant digitalis.

Gastrointestinal

Gastrointestinal side effects have most commonly included dry mouth (30%) and constipation (15%), abdominal pain, anorexia, nausea, vomiting, diarrhea (1%), parotitis, pseudo-obstruction (including colonic pseudo-obstruction), and salivary gland pain. Nausea (13.2%) and vomiting (10.5%) have been reported with epidural clonidine.

Genitourinary

Genitourinary side effects have included impotence in male patients (24%), retrograde and delayed ejaculation, and an inability to achieve orgasm in female patients.

Dermatologic

Dermatologic reactions have been reported in 10% to 38% of patients who use transdermal clonidine. These

reactions include psoriasis exacerbations, local dermatitis and/or pigmentation, alopecia, angioneurotic edema, hives, pruritus, rash, and urticaria.

Psychiatric

Psychiatric side effects have included emotional disorder (5%), aggression (1%), tearfulness (3%) and rare reports of depression, which has been the most common psychiatric reaction to clonidine. Rare cases of frank psychoses and delirium have been associated with clonidine withdrawal.

Endocrine

Endocrinologic side effects have been limited to rare cases of gynecomastia, hyperprolactinemia, or hyperglycemia.

Musculoskeletal

Musculoskeletal side effects have included leg cramps and muscle or joint pain. Moderately severe myalgia has been associated with the use of clonidine in patients treated for opioid withdrawal symptoms.

Immunologic

Immunologic side effects have rarely been reported and include one case of immune-complex disease.

Respiratory

Respiratory system reactions have included nasal congestion (5%), asthma (1%), and nasopharyngitis (3%). A case of severe bronchospasm associated with clonidine has been reported in the pediatric literature.

Ocular

Ocular side effects have included accommodation disorder, blurred vision, burning of the eyes, decreased lacrimation, and dryness of the eyes.

Metabolic

Metabolic side effects have included thirst (3%) and throat pain (6%).

A study of 13 patients who had pre- and post-clonidine cerebral blood flow (CBF) measured by nuclear scanning revealed that patients with an initially high pretreatment CBF tended to demonstrate decreased CBF after clonidine therapy.

Patients with traumatic spinal cord injury receiving clonidine may experience a delayed-onset of sedation regardless of the route of administration (i.e., intrathecal, intramuscular).

A case of sinus arrest associated with clonidine has been reported. A 65-year-old man with diabetes, hypertension and unexplained syncope developed more frequent syncope and dizziness associated with documented episodes of sinus arrest during the first week of clonidine therapy. The patient had no hypoglycemia or orthostatic changes. The syncope and dizziness resolved upon discontinuation of clonidine; continuous electrocardiographic monitoring revealed a gradual and complete disappearance of sinus pauses. Junctional bradycardia and AV heart block have also been reported.

Ventricular tachycardia (VT) relatively refractory to lidocaine, but responsive to intravenous phentolamine, has

been associated with clonidine withdrawal (case report). The authors believe that the VT was probably produced by humoral or neural stimulation of unregulated myocardial alpha-adrenergic receptors.

Transdermal clonidine has been implicated with hypertension in a quadriplegic patient with a C4 spinal lesion. The proposed mechanism is predominance of clonidine's peripheral alpha-1 adrenergic effects due to the patient's autonomic dysfunction, resulting in vasoconstriction and hypertension.

Sinus bradycardia or other supraventricular bradyarrhythmias are more likely in patients with underlying renal dysfunction.

In one case report, severe hypotension occurred during separation from cardiopulmonary bypass in a patient given intrathecal clonidine. The patient responded to volume expansion and use of vasoconstrictors.

A 66-year-old woman with a history of psoriasis in remission developed erythematous, scaly plaques on the extensor surfaces of her forearms within three days after beginning clonidine therapy for control of flushing. The author of this case report suspected that clonidine may cause a fall in intracellular cAMP, leading to epidermal cell proliferation, and, in some cases, a psoriasiform eruption.

A 68-year-old black man with hypertension, status post unilateral nephrectomy, was incidentally found to have 4+ proteinuria, 1+ glycosuria, new elevated blood glucose levels, and between 1.8 and 5.4 grams of protein per 24-hour urine collection within 6 weeks after starting clonidine. The signs and symptoms of diabetes and the nephrotic syndrome disappeared within five months after discontinuation of clonidine. Because of his solitary kidney, a renal biopsy was not performed.

A 46-year-old woman developed forearm edema, mild thenar atrophy, and skin hypopigmentation within three months after beginning clonidine for perimenopausal flushing. Electromyelography was consistent with carpal tunnel syndrome. At surgical decompression, a skin biopsy revealed changes consistent with immune-complex disease. The patient's signs and symptoms abated after physical therapy and discontinuation of clonidine.

A 9-year-old boy with asthma developed a severe asthma attack after an oral clonidine stimulation test. He required hospitalization. The authors of this case report suspect that clonidine may have caused acute pulmonary artery vasoconstriction (directly), which could have decreased pulmonary blood flow, producing relative pulmonary hypoxemia, setting off an asthma attack.

IV Compatibility (Top)

DESCRIPTION

D10W	D5¼S	D5½S	D5LR	D5NS	D5R	D5W	LR	NS	R	SODLAC	UNSP

Clonidine is a clear, colorless, preservative-free aqueous sterile solution, with a pH of 5-7. Undiluted clonidine should be stored at 15-30°C (1815).

STABILITY

D10W	D5¼S	D5½S	D5LR	D5NS	D5R	D5W	LR	NS	R	SODLAC	UNSP
								C			

Clonidine, 0.15 mg/ml, 0.5 mg/ml, or 1.5 mg/ml, in NS, was stable for up to 24 months at 4°C or 23°C (1579). Clonidine, 0.2 mg/ml, in NS, was stable for at least 10 weeks when stored at 37°C (1853).

Clonidine, 9 µg/ml, in NS, was physically compatible in polypropylene syringes for 30 days at 4°C, 21°C, and 35°C. However, clonidine stored at 35°C in syringes with a latex-free polyisoprene piston exhibited a pH shift outside the acceptable pH range (1897).
Formulation of clonidine, 150 mg, in NS 100 ml, in tight, light-resistant container was physically compatible (1975).

Source: *King's (R) Guide to Parenteral Admixtures (R)*

Dosage (Top)

Usual Adult Dose

Hypertension

Initial dose (PO): 0.1 mg orally twice a day (morning and bedtime).
Maintenance dose: 0.2 to 0.6 mg/day given in divided doses.

Initial dose (patches):Clonidine TTS-1 (0.1 mg/24 hr) applied once a week.
Maintenance dose: If after 1 to 2 weeks the desired reduction in blood pressure is not achieved, increase the dosage by adding another TTS-1 film or changing to a larger system.
An increase in dosage above 2 clonidine TTS-3 films is usually not associated with additional efficacy.

Extended-release tablets:
Initial dose: 0.17 mg orally once daily at bedtime. Further increments of 0.09 mg orally once daily may be made at weekly intervals if necessary until the desired response is achieved.
Maintenance dose: 0.17 mg to 0.52 mg orally once daily at bedtime

Extended-release oral suspension:
Initial dose: 0.17 mg (2 mL) orally once daily at bedtime. Further increments of 0.09 mg (1 mL) orally once daily may be made at weekly intervals if necessary until the desired response is achieved.
Maintenance dose: 0.17 mg to 0.52 mg orally once daily at bedtime

Pain

Continuous Epidural Infusion:
Initial dose: 30 mcg/hr.
May be titrated up or down depending on pain relief and occurrence of adverse events.
Maximum dose 40 mcg/hr.

Pheochromocytoma Diagnosis

0.3 mg orally once. Clonidine is only recommended after baseline determination of plasma catecholamines. Two baseline samples can be obtained five minutes apart from an existing IV line after the patient has remained supine for 90 minutes (a new needle stick could increase catecholamine concentrations and foul the test).

After the initial dose of clonidine, three additional hourly blood samples may be obtained for plasma catecholamine concentration measurements.

Generally, patients with hypertension and pheochromocytoma do NOT show a decrease in plasma catecholamine levels after this "suppression test", whereas hypertensive patients without pheochromocytoma do. False negative tests have been reported.

Hypertensive Emergency

0.2 mg orally once. Additional doses of 0.1 mg may be given as needed and tolerated every hour to control this patient's blood pressure. Be cognizant of the risk of stroke or heart attack or other problem associated with aggressive blood pressure reduction, especially in older persons. The maximum recommended total daily dose in any case of emergent hypertension is 0.8 mg.

Some clinicians report a poor antihypertensive effect of clonidine in patients with spinal injuries since this drug acts on the central nervous system to inhibit peripheral sympathetic tone, and the central and peripheral nervous systems are disrupted in these patients.

Alcohol Withdrawal

0.1 mg orally twice a day or TTS-1 (0.1 mg) transdermal patch once a week.

Anxiety

0.1 mg orally twice a day or TTS-1 (0.1 mg) transdermal patch once a week.

Benzodiazepine Withdrawal

0.1 mg orally twice a day or TTS-1 (0.1 mg) transdermal patch once a week.

Bipolar Disorder

0.1 mg orally twice a day or TTS-1 (0.1 mg) transdermal patch once a week.

Migraine Prophylaxis

0.1 mg orally twice a day or TTS-1 (0.1 mg) transdermal patch once a week.

Perimenopausal Symptoms

0.1 mg orally twice a day or TTS-1 (0.1 mg) transdermal patch once a week.

Smoking Cessation

0.1 mg orally twice a day or TTS-1 (0.1 mg) transdermal patch once a week.

Opiate Withdrawal

0.2 mg orally twice a day or TTS-2 (0.2 mg) transdermal patch once a week.

Usual Pediatric Dose

Not applicable

Dosing is expressed as the salt (clonidine hydrochloride) unless otherwise noted. Formulations of clonidine (immediate release versus extended release) are not interchangeable on a mg per mg basis due to different pharmacokinetic profiles. This includes commercially available oral suspension (Nexiclon XR {R}) which is an extended release preparation and should not be used interchangeably with any extemporaneously prepared clonidine oral suspension.

Neonatal abstinence syndrome (opioid withdrawal): (Limited information; further studies needed):
Oral:
Preterm neonate: 0.5 to 1 mcg/kg/dose every 6 hours was used in 14 neonates (median gestational age: 26 weeks and 2 days; range: 24 to 40 weeks) with either iatrogenic opioid dependency or neonatal abstinence syndrome; clonidine was stopped or tapered by 0.25 mcg/kg every 6 hours once patients were stabilized.
Full-term neonate: 1 mcg/kg/dose every 4 hours in combination with diluted opium tincture. A randomized, controlled, comparative trial in 80 neonates (GA: ≈35 weeks) with neonatal abstinence syndrome demonstrated a decreased length of therapy and opioid doses in the combination treatment (clonidine plus diluted opium tincture) as compared to diluted tincture of opium alone. Another report of 7 infants reported success in six using an initial dose of 0.5 to 1 mcg/kg/dose followed by 3 to 5 mcg/kg/day divided every 4 to 6 hours.

Hypertension (unlabeled use):
Oral:
Children and Adolescents 1 to 17 years:
Immediate release:
Initial dose: 5 to 10 mcg/kg/day orally in divided doses every 8 to 12 hours. Increase gradually as needed
Usual range: 5 to 25 mcg/kg/day in divided doses every 6 hours
Maximum dose: 0.9 mg/day orally
Alternate dosing:
Oral:
Children greater than or equal to 12 years:
Immediate release:
Initial dose: 0.1 mg/day orally 2 times a day. Increase gradually, if needed, in 0.1 mg/day increments at weekly intervals
Usual maintenance dose: 0.2 to 0.6 mg/day in divided doses
Maximum dose: 2.4 mg/day orally (rarely required)
Transdermal: Children and Adolescents: May be switched to the transdermal delivery system after oral therapy is titrated to an optimal and stable dose; a transdermal dose approximately equivalent to the total oral daily dose may be used.

Severe hypertension (unlabeled use):
Oral:
Children and Adolescents 1 to 17 years:
Immediate release: 0.05 to 0.1 mg/dose orally. May repeat up to a maximum total dose of 0.8 mg orally.

Clonidine tolerance test (test of growth hormone release from pituitary) (unlabeled use):
Oral: 0.15 mg/m2 orally as a single dose
or
5 mcg/kg orally as a single dose
Maximum dose: 250 mcg orally

Neuropathic pain (unlabeled use):
Oral:
Children and Adolescents:
The following doses have been used:
Initial: 2 mcg/kg/dose every 4 to 6 hours, increased incrementally over several days
Range: 2 to 4 mcg/kg/dose every 4 to 6 hours
Transdermal: Children and Adolescents: May be switched to the transdermal delivery system after oral therapy is titrated to an optimal and stable dose; a transdermal dose approximately equivalent to the total oral daily dose may be used.

Tic disorders and Tourette's syndrome (unlabeled use):

Initial: 0.025 to 0.05 mg/day with gradual titration to 3 to 4 times daily using small increments (0.025 mg)
Target daily dose: 0.2 to 0.3 mg/day; doses up to 0.4 mg/day have been reported

Attention Deficit Disorder

May be used alone or as an adjunct to stimulants.

Immediate release (unlabeled indication):
Children less than or equal to 45 kg:
Initial dose: 0.05 mg orally at bedtime. Increase sequentially every 3 to 7 days by 0.05 mg increments as 2 times daily, then 3 times daily, then 4 times daily.
Maximum dose: 0.2 mg/day orally for patients weighing 27 to 40.5 kg; 0.3 mg/day for patients weighing 40.5 to 45 kg.
When discontinuing therapy, taper gradually over 1 to 2 weeks.

Children greater than 45 kg:
Initial dose: 0.1 mg orally at bedtime. Increase sequentially every 3 to 7 days by 0.1 mg increments as 2 times daily, then 3 times daily, then 4 times daily
Maximum dose: 0.4 mg/day
When discontinuing therapy, taper gradually over 1 to 2 weeks.

Extended release (Kapva {R}):
Children greater than or equal to 6 years:
Initial dose: 0.1 mg orally at bedtime. Increase in 0.1 mg/day increments every 7 days until desired response. Doses should be administered twice daily (either split equally or with the higher split dosage given at bedtime).
Maximum dose: 0.4 mg/day orally
Note: Maintenance treatment for greater than 5 weeks has not been evaluated.
When discontinuing therapy, taper daily dose by less than or equal to 0.1 mg every 3 to 7 days.
Transdermal: Children may be switched to the transdermal delivery system after oral therapy is titrated to an optimal and stable dose; a transdermal dose approximately equivalent to the total oral daily dose may be used.

The dose of clonidine extended-release tablets, administered either as monotherapy or as adjunctive therapy to a psychostimulant, should be individualized according to the therapeutic needs and response of the patient. Dosing should be initiated with one 0.1 mg tablet at bedtime, and the daily dosage should be adjusted in increments of 0.1 mg/day at weekly intervals until the desired response is achieved. Doses should be taken twice a day, with either an equal or higher split dosage being given at bedtime.

Additional Dosage (Top)

Renal Dose Adjustments

Doses should be titrated up slowly in patients with renal dysfunction.

CrCl less than 10 mL/min: The dose should be reduced by 50% to 75% of the normal initial dose.

For extended-release tablets and oral suspension: Adjust dosage according to the degree of impairment. In patients with end stage kidney disease on maintenance dialysis, start at 0.09 mg per day and titrate up slowly to minimize dose related adverse events.

Liver Dose Adjustments

Data not available

Dose Adjustments

Elderly patients may benefit from a lower initial dose.

Dosing adjustments of 0.1 mg/day, may be made at weekly intervals if necessary until the desired response is achieved.

When switching from immediate-release to extended-release tablets:
Initial dose: Substitute 0.17 mg extended-release orally once daily for 0.1 mg immediate-release orally twice daily
Maintenance dose titration increments: Substitute 0.09 mg extended-release orally once daily for 0.05 mg immediate-release orally twice daily
Maintenance doses: Substitute 0.17 mg extended-release orally once daily for 0.1 mg immediate-release orally twice daily, or 0.34 mg extended-release orally once daily for 0.2 mg immediate-release orally twice daily, or 0.52 mg extended-release orally once daily for 0.3 mg immediate-release orally twice daily.

When switching from immediate-release tablets to extended-release oral suspension:
Initial dose: Substitute 0.17 mg (2 mL) extended-release orally once daily for 0.1 mg immediate-release orally twice daily
Maintenance dose titration increments: Substitute 0.09 mg (1 mL) extended-release orally once daily for 0.05 mg immediate-release orally twice daily
Maintenance doses: Substitute 0.17 mg (2 mL) extended-release orally once daily for 0.1 mg immediate-release orally twice daily, or 0.34 mg (4 mL) extended-release orally once daily for 0.2 mg immediate-release orally twice daily, or 0.52 mg (6 mL) extended-release orally once daily for 0.3 mg immediate-release orally twice daily.

Precautions

When substituting clonidine topical film for oral clonidine or for other antihypertensive drugs, the antihypertensive effect of clonidine topical film may not commence until 2 to 3 days after initial application. Therefore, gradual reduction of prior drug dosage is advised. Some or all previous antihypertensive treatment may have to be continued, particularly in patients with more severe forms of hypertension.

Patients should not discontinue therapy without consulting a physician. Dose reduction should be performed gradually over a 2 to 4 day period to avoid withdrawal symptomatology. Rare instances of hypertensive encephalopathy, cerebrovascular accidents and death have been reported after clonidine withdrawal.

Patients with severe coronary insufficiency, conduction disturbances, recent myocardial infarction, cerebrovascular disease, or chronic renal failure should have their dosage titrated up slowly.

In perioperative use, clonidine extended-release tablets and suspension may be administered up to 28 hours prior to surgery and resumed the following day.

Clonidine extended-release tablet formulation is dosed twice a day, the same as the immediate-release clonidine formulation, but it is not to be used interchangeably with the immediate-release formulation.

Clonidine extended-release tablets must be swallowed whole and never crushed, cut or chewed.

Clonidine extended-release tablets may be taken with or without food.

Due to the lack of controlled clinical trial data and differing pharmacokinetic profiles, substitution clonidine

extended-release tablets for other clonidine products on a mg-per-mg basis is not recommended.

Elderly patients may benefit from a lower initial dose of clonidine.

Safety and effectiveness of clonidine immediate-release, patches, extended-release tablets, and extended-release suspension have not been established in pediatric patients (less than 18 years of age). Safety and effectiveness of clonidine extended-release tablets have not been studied in children with ADHD less than 6 years old.

Dialysis

Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental clonidine following dialysis.

Other Comments

Taking the larger portion of the oral daily dose at bedtime may minimize transient adjustment effects of dry mouth and drowsiness. In addition, administration at bedtime may minimize the risk of morning-associated cardiovascular events (i.e., stroke, transient ischemic attacks, myocardial infarction, or sudden cardiac death). Studies have indicated that 2.4 mg is the maximum effective daily dose, but doses as high as this have rarely been employed.

Apply clonidine topical film once every 7 days to a hairless area of intact skin on the upper outer arm or chest. Each new application of should be on a different skin site from the previous location. If the system loosens during 7-day wearing, the adhesive overlay should be applied directly over the system to ensure good adhesion. There have been rare reports of the need for patch changes prior to 7 days to maintain blood pressure control.

The effectiveness of clonidine extended-release tablets for longer-term use (more than 5 weeks) has not been systematically evaluated in controlled trials. Therefore the physician electing to use clonidine extended-release tablets for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

When discontinuing clonidine extended-release tablets, the total daily dose should be tapered in decrements of no more than 0.1 mg every 3 to 7 days.