Central Sympatholytic Drugs

Wanpen Vongpatanasin, MD;[1] Kazuomi Kario, MD, PhD;[2] Steven A. Atlas, MD;[3] Ronald G. Victor, MD[4]

From the Hypertension Section, University of Texas Southwestern Medical Center, Dallas, TX;[1] Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan;[2] James J. Peters VA Medical Center and Department of Medicine, Mount Sinai School of Medicine, Bronx, NY;[3] and the Heart Institute, Cedars Sinai Medical Center, Los Angeles, CA[4]

Key Points

- Central sympatholytic drugs reduce blood pressure mainly by stimulating central α_2-adrenergic receptors in the brainstem centers, thereby reducing sympathetic nerve activity and neuronal release of norepinephrine to the heart and peripheral circulation.
- This class of drugs, however, is currently used mainly as fourth-line (or beyond) drug therapy for hypertension because of side effects of drowsiness, fatigue, and dry mouth.
- Rebound hypertension is also another major concern in certain drugs with a short half-life, particularly in patients who are nonadherent to the regimen. Therefore, their use on a ''PRN'' basis for treatment of blood pressure surge in the absence of symptoms or acute target complications should also be avoided. *J Clin Hypertens (Greenwich).* 2011;13:658–661. ©2011 Wiley Periodicals, Inc.

Central sympatholytic agents were first introduced into clinical use in the 1960s. α-Methyldopa, the first drug to be widely used, is the only prodrug in this class. It is converted to α-methylnorepinephrine, which was at first thought to act peripherally as a false neurotransmitter. Clonidine, the prototype of the second-generation drugs in this class, all of which are imidazoline derivatives, was initially developed as a nasal decongestant because of its potential vasoconstrictor effect via postsynaptic α_2-adrenergic receptor (AR) stimulation but was surprisingly found to have antihypertensive effects via activation of presynaptic α_2-AR in the brainstem.[1] A similar effect of centrally formed α-methylnorepinephrine is now understood to account for the blood pressure (BP)–lowering effect of methyldopa. Subsequently, other direct-acting central sympatholytic drugs such as guanfacine and guanabenz were approved for treatment of hypertension in the United States. Moxonidine and rilmenidine are also centrally acting drugs used in England and other European countries but are not available in the United States. In contrast to clonidine and other α_2 agonists, moxonidine and rilmenidine predominantly reduce sympathetic nerve activity (SNA) and BP by stimulating imidazoline-1 (I_1) receptor, rather than α_2-AR in the brainstem.[2]

PHARMACOLOGY

The pharmacokinetic profile of central sympatholytic agents is shown in the Table. Central sympatholytic drugs reduce BP mainly by activation of α_2-AR in the rostral ventrolateral medulla (Figure), resulting in decreased SNA[3,4] and, to a lesser extent, by inhibition of presynaptic release of norepinephrine from peripheral sympathetic nerve terminals.[3] Activation of I_1 receptors in the brainstem centers also contributes to sympatholytic action and BP-lowering effects of all the second-generation drugs (ie, except for methyldopa), independent of central α_2-ARs.[5] Clonidine activates both I_1 receptors and α_2-ARs. Guanfacine and guanabenz are more selective for α_2-AR than clonidine.

CLONIDINE

Clonidine has been approved for treatment of hypertension in the United States since 1974. Following oral administration, plasma levels of clonidine peak in approximately 1 to 4 hours and the plasma half-life ranges from 6 to 16 hours.[6,7] The half-life increases up to 41 hours in patients with severe impairment of renal function. About 40% to 60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours. About 50% of the absorbed dose is metabolized in the liver. An antihypertensive effect of clonidine is usually observed within 30 to 60 minutes after an oral dose. The peak effect occurs within 2 to 4 hours, with a duration of action lasting for approximately 6 to 8 hours.[6] Therefore, the drug should be given 2 to 3 times a day.

Treatment with oral clonidine has been shown to decrease resting cardiac output by 15% to 20% without affecting total peripheral resistance (TPR) in hypertensive patients.[8,9] Reduction in heart rate, rather than stroke volume, is mainly responsible for decreased resting cardiac output. Reduction in plasma renin activity and urinary aldosterone excretion is also observed after clonidine, likely related to reduction in renal SNA.[9–11]

Clonidine can also be administered via a 7-day transdermal system. Plasma clonidine levels increase more gradually with the clonidine patch than with oral

Address for correspondence: Wanpen Vongpatanasin, MD, Hypertension Section, Cardiology Division, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, U9.400 Dallas, TX 75390-8586
E-mail: wanpen.vongpatanasin@utsouthwestern.edu

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TABLE. Dose Range and Pharmacokinetics of Central Sympatholytic Drugs

Drug	Total Dose Range, mg/d	Doses Per Day	T_{max}, h	Half-Life, h	Renal Elimination, %
Clonidine	0.2–1.2	2–3	1–4	6–16	40–60
Clonidine patch	0.1–0.6	Weekly	72	14–26	40–60
Guanabenz	8–32	2	2–5	6–14	<5
Guanfacine	1–3	1	1–4	10–30	50
Methyldopa	250–2000	2	2–4	1–2	70
Moxonidine[a]	0.2–0.6	1–2	1.0–1.5	2–3	50–75
Rilmenidine[a]	1–2	1	1.7	8.5	52–93

Abbreviation: T_{max}, time to peak plasma concentration. [a]Not available in the United States.

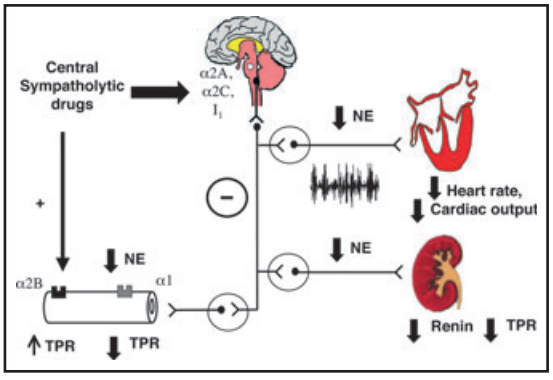

FIGURE. Illustration of the mechanisms underlying cardiovascular effects of central sympatholytic drugs. Central sympatholytic drugs inhibit central sympathetic discharge via activation of α_2A, α_2C, or imidazoline 1 (I_1) receptors in the brainstem, resulting in decreased heart rate, cardiac output, and total peripheral resistance (TPR). Activation of prejunctional α_2A and α_2C receptors causing inhibition of norepinephrine (NE) release from peripheral sympathetic nerve terminals also contributes to reduction in blood pressure (not shown in the Figure). Activation of α_2B receptors, which are located postjunctionally in the vascular smooth muscle may cause transient vasoconstriction and blood pressure elevation during rapid drug administration.

clonidine, reaching steady-state concentration within 3 days of application.[12] When the patch is removed, plasma clonidine concentration remains unchanged for 8 to 12 hours, suggesting that skin acts as a temporary drug reservoir.[11,12] BP-lowering effects of the transdermal system are comparable to that with the oral route. However, skin reactions are a troublesome side effect of the clonidine patch, occurring in 20% to 25% of patients.[13] Pretreatment with hydrocortisone cream may reduce the incidence of dermatitis without affecting clonidine delivery to the circulation.[14]

Abrupt cessation of clonidine is known to precipitate symptoms of sympathetic overactivity, such as anxiety, tremor, headache, palpitation, and rebound hypertension within 36 to 72 hours of discontinuation.[15,16] A rise in BP above pretreatment values is less common. Nevertheless, oral clonidine should be gradually weaned when therapy is discontinued and it should not be given as a once-daily regimen or on an as-needed basis. Rebound hypertension occurs less frequently with the transdermal system because of more gradual reduction in clonidine levels. The rebound phenomenon may be exaggerated in patients concurrently treated with β-AR blockers due to unopposed α-adrenergic vasoconstriction, and β-AR blockade should never be initiated by itself in withdrawing patients. Therapy for rebound includes treatment with α-AR blockers (or with combined α- and β-AR blockers if tachycardia is severe) or reinstitution of clonidine.

GUANFACINE

Guanfacine is an α_2 agonist with 12 to 25 times higher selectivity than clonidine for the α_2-AR vs the α_1-AR.[17,18] In individuals with normal renal function, the average elimination half-life is approximately 17 hours. Peak plasma concentrations occur from 1 to 4 hours after single oral doses. Steady-state blood levels are achieved within 4 days in most patients. In contrast to clonidine, studies in hypertensive patients have suggested that guanfacine reduces BP mainly by reducing total vascular resistance rather than cardiac output.[19,20] Guanfacine reduces resting heart rate with minimal effect on heart rate during exercise.[19] In contrast, guanfacine reduces TPR similarly both at rest and during exercise with minimal effects on cardiac output.[19] Guanfacine is typically administered once daily at bedtime. Most of the side effects of guanfacine, such as dry mouth, sedation, and fatigue, are similar to those seen with clonidine. Rebound hypertension, however, occurs less frequently than clonidine because of its longer half-life.[21] Although guanfacine is US Food and Drug Administration–approved only for treatment of hypertension, it has also been used for treatment of attention deficit/hyperactivity disorder in children and young adults.[22]

α-METHYLDOPA

In contrast to clonidine and guanfacine, α-methyldopa does not directly reduce BP but, as noted earlier, first requires conversion to α-methylnorepinephrine in the central nervous system, which, in turn, leads to activation of central α_2-ARs and inhibition of sympathetic outflow. Oral bioavailability of methyldopa is about 25%, with an average time to reach maximum plasma concentration of 2 hours. Half-life on average is

between 1 and 2 hours in healthy patients and hypertensive patients[23,24] but is increased to 4 to 6 hours in patients with renal failure, resulting in a prolonged hypotensive action in these patients.[25] Following oral administration, an effect of α-methyldopa on BP is detectable within 1 hour, reaching a peak effect within 6 to 8 hours.[23] Plasma renin activity is also reduced during α-methyldopa treatment.[26] The usual daily dosage of α-methyldopa is 500 mg to 2 g, divided into 2 to 4 doses. In hypertensive patients, methyldopa reduces BP mainly by reducing TPR with minimal effects on heart rate or cardiac output.[23] Although once a mainstay of antihypertensive therapy, α-methyldopa is currently used mainly in pregnant women with hypertension because of lack of teratogenicity or fetal side effects. Maternal cardiac output, uterine blood flow, and renal blood flow are also unaffected by α-methyldopa.[27] Side effects of α-methyldopa requiring drug discontinuation are relatively infrequent. Sedation and fatigue may occur but are usually transient. Other side effects include positive Coombs test, drug-induced fever, and pancreatitis, hemolytic anemia, hepatic dysfunction, nasal congestion, exacerbation of Parkinsonism, hyperprolactinemia, and gynecomastia.

GUANABENZ

Guanabenz is another direct central α_2-agonist, which is predominantly eliminated via hepatic biotransformation.[28,29] Thus, unlike clonidine, dose adjustment is not required in patients with renal failure but required in those with chronic liver diseases. Guanabenz has been shown to be effective in reducing left ventricular hypertrophy in hypertensive patients[4] and in attenuating morning hypertension when administered at nighttime.[30] The half-life of guanabenz is between 12 and 14 hours and the drug is typically given twice daily at a dosage between 8 mg/d and 32 mg/d.[31] Side effects of guanabenz are similar to those of clonidine.[31]

SUMMARY

Central sympatholytic drugs are effective in lowering BP by decreasing sympathetic outflow to the heart and peripheral circulation. Long-term use of central sympatholytic drugs has been shown to reduce target organ complications but it is unclear whether these drugs reduce cardiovascular risk beyond their BP-lowering effect. Perioperative use of central α_2-agonists in patients with high cardiovascular risk undergoing cardiac or noncardiac surgery appears to reduce cardiac complications and should be considered in patients who cannot tolerate β-blockers. Because of lack of clear-cut cardiovascular benefit and several major side effects, including fatigue, sedation, and dry mouth, these drugs should be used as fourth-line drug therapy for hypertension. Central sympatholytic drugs should also be used cautiously in patients with autonomic failure with supine hypertension due to a potential direct vasoconstrictor effect mediated by vascular postsynaptic α_2 receptors. Central sympatholytic drug use should be avoided in patients who are nonadherent to treatment because of precipitation of withdrawal symptoms on abrupt drug discontinuation. Their use on a "PRN" basis for treatment of episodes of BP elevation in the absence of symptoms or acute target complications should also be discouraged because of potential rebound hypertension. In patients who are adherent to treatment, central sympatholytic drugs remain an important add-on therapy for hypertension, particularly if associated with overactivation of the sympathetic nervous system (usually characterized by elevated heart rate or cardiac output)[32] or for hypertension associated with impairment in carotid or aortic baroreceptor–mediated inhibition of central sympathetic outflow.[33]

OTHER SYMPATHOLYTIC DRUGS

Reserpine has been extensively used in the past as an effective antihypertensive agent especially at lower doses and combined with thiazide-type diuretics.[34,35] Unlike sympatholytic drugs mentioned above, reserpine reduces BP by depleting norepinephrine stores in the peripheral postganglionic sympathetic nerve terminals without reducing central sympathetic discharge.[36] Although higher doses (0.75 mg/d to 10 mg/d) have been associated with significant side effects, including nasal stuffiness, peptic ulcer disease, and depression, its long action and effectiveness make it an available useful agent for antihypertensive therapy, particularly at lower doses (0.1 mg/d to 0.5 mg/d).[34,35]

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