

Current Concepts of Pharmacotherapy in Hypertension

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Centrally Acting Antihypertensive Agents: An Update

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Centrally acting agents stimulate α_2 receptors and/or imidazoline receptors on adrenergic neurons situated within the rostral ventrolateral medulla and, in so doing, sympathetic outflow is reduced. Centrally acting agents also stimulate peripheral α_2 receptors, which, for the most part, is of marginal clinical significance. Central α agonists have had a lengthy history of use, starting with α -methyldopa, which has had a dramatic decline in use, in part, because of bothersome side effects. Patients who require multidrug therapy with otherwise resistant hypertension, such as diabetic and/or renal failure patients, are typically responsive to these drugs, as are patients with sympathetically driven forms of hypertension. Perioperative forms of hypertension respond well to clonidine, a circumstance where the additional anesthesia- and analgesia-sparing effects of this drug may offer additional clinical benefits. Clonidine can be used adjunctively with other more traditional therapies in heart failure, particularly when hypertension is present. Sustained-release moxonidine, however, is associated with early mortality and morbidity when used in patients with heart failure. Escalating doses of drugs in this class often give rise to salt and water

retention, in which case diuretic therapy becomes a valuable adjunctive therapy. (J Clin Hypertens. 2007;9:399–405) ©2007 Le Jacq

Although complex and incompletely understood, a linkage exists between the centrally moderated, activated sympathetic nervous system (SNS) and hypertension. SNS activation is also an important factor in heart failure (HF) and moreover it has bearing on various developmental aspects of the metabolic syndrome. In more general terms, sympathetic activation, as reflected by an increase in both heart rate and/or plasma catecholamine levels, is considered a determinant of hypertension and thus a target with considerable potential for drug treatment; however, centrally acting antihypertensive agents still prove effective even in the absence of apparent signs of SNS activation.^{1,2} Of note, SNS activity need not be measurably abnormal but rather can perpetuate the hypertensive state if merely increased (albeit inappropriately so) relative to a patient's particular hemodynamic, volume, and neurohumoral circumstances. In addition, the SNS is adjoined to other regulatory pathways in a manner such that even a normal level of activity can disproportionately contribute to the prevailing blood pressure (BP). This is particularly the case when the relationship between the sympathetic and renin-angiotensin systems is considered. It has been estimated that as many as 30% of essential hypertension patients have a primary neurogenic stimulus contributing to their hypertension.³

MECHANISM OF ACTION

Molecular Aspects of Drug Action and Pharmacokinetics

The antihypertensive action of α -methyldopa was originally believed to be via tissue inhibition of

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DRUG	VOLUME OF DISTRIBUTION, L/KG	ABSORPTION, %	T _{MAX} , H	HALF-LIFE, H	PROTEIN-BINDING, %
α -Methyldopa	0.6	25	2.0	1.7	<15
Clonidine	2.0	75–100	1.5–2.0	6–15	20–40
Guanabenz	7.4–13.4	75	2–5	6–14	90
Guanfacine	6.3	>90	1.5–4.0	17	70
Moxonidine*	3.0	80–90	0.5–3.0	2–3	5.8–7.9
Rilmenidine*	315–325	100	1.7	8.5	10–11

*Not available in the United States.

DRUG	RENAL ELIMINATION, %*	DIALYZABILITY	DOSE ADJUSTMENT IN RENAL FAILURE	FDA PREGNANCY CATEGORY
α -Methyldopa	70	Yes	Yes	C
Clonidine	58	Yes, but limited	No	C
Guanabenz	<5	No	No	C†
Guanfacine	50	Limited	No	B‡
Moxonidine§	50–75	Not known	Yes	Not classified
Rilmenidine§	52–93	Yes	Yes	Not classified

*Elimination of the intact molecule. †Food and Drug Administration (FDA) category C: Studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women. Drugs should be given only if the potential benefit justifies the potential risk to the fetus. ‡FDA category B: Animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, and animal studies have shown adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters). §Not available in the United States, thus, there is no basis for FDA pregnancy categorization.

dopa decarboxylase with an ensuing depletion of biogenic amines; however, this mechanism plays a minimal role in its BP-lowering effect. Instead, α -methyldopa lowers BP by conversion to the active metabolite α -methylnorepinephrine (eg, the concept of a false neurotransmitter), which dislodges norepinephrine from α -adrenergic receptors.⁴ The other agents in this class do not require metabolic conversion and are active as intact molecules. For the main pharmacodynamic effect of compounds in this class to occur, drugs must pass the blood-brain barrier. As such, there is an implicit time lag between achieved plasma drug concentrations and an antihypertensive effect. The pharmacokinetics of the various centrally acting agents are similar but with a few noteworthy exceptions (Table I and Table II).

The onset of action varies among the compounds in this class, with clonidine showing meaningful activity within 15 to 30 minutes of intake. These compounds typically have a large volume of distribution, which, in part, relates to their distribution in the central nervous system. The systemic half-life for compounds in this class can vary substantially from pharmacodynamic half-life. This finding relates to receptor affinity and depot effects in deep-tissue compartments. Finally, moxonidine and rilmenidine (both of these

compounds are not available in the United States) undergo extensive renal clearance, which requires that they be carefully dose-adjusted in the patient with renal failure.^{5,6}

Pharmacodynamics

Centrally acting drugs stimulate central vasomotor adrenergic receptors (eg, nucleus tractus solitarii) and, in so doing, central sympathetic outflow to both the heart and peripheral vasculature is inhibited. Plasma catecholamine levels decrease with centrally acting therapy, which may relate, in part, to their stimulation of peripherally located presynaptic α_2 receptors. Clonidine stimulates both α_2 receptors and imidazoline (I_1) receptors as the basis for its peripheral sympathoinhibition.⁷ Guanfacine is considered a more selective α_2 receptor agonist than clonidine. Unlike clonidine, guanfacine does not inhibit dopamine turnover.

The physiologic effects of withdrawal of SNS tone include parallel and balanced falls in peripheral vascular resistance and systolic/diastolic BP. The reduction in peripheral resistance that is seen with centrally acting agents persists during long-term treatment. Despite the vasodilator action of drugs in this class, reflex tachycardia does not develop and, in point-of-fact, heart rate may be somewhat reduced in the course of treatment. Cardiac output

and renal blood flow typically go unaffected with drugs in this class.⁸ Also, during exercise, these compounds still maintain a reduced peripheral vascular resistance, which implies that usual exercise-related changes in SNS activity are blocked.⁹ Centrally acting agents also reduce plasma renin activity and, with long-term treatment, left ventricular hypertrophy will regress.¹⁰ Agents in this class tend to produce dose-dependent salt and water retention and as a result their effectiveness may diminish over time. This pseudotolerance to a BP-lowering effect can be undone with diuretic therapy.

INDICATIONS/CONTRAINDICATIONS AND OBJECTIVES OF THERAPY

Indications

The antihypertensive efficacy of both central α_2 receptor and I_1 receptor agonists is well-established. Clonidine, the standard in this class, has been shown in the Veterans Affairs Cooperative Study¹ to be an effective antihypertensive drug, particularly in whites and older blacks. Centrally acting compounds compare favorably in effectiveness with first-line antihypertensive drug classes, such as diuretics, angiotensin-converting enzyme inhibitors, and calcium channel blockers. These compounds, however, probably find their greatest use as adjunct therapy to other antihypertensive medication classes. This is particularly the case when reflex sympathetic activation, as occurs with vasodilators such as hydralazine and minoxidil, needs to be checked.

Centrally acting compounds are especially useful in those patients with labile hypertension marked by a significant component of anxiety. Drugs in this class can be used safely in patients with diabetes without any meaningful loss of glycemic control. Patients with pulmonary diseases, such as asthma, also safely tolerate these compounds.¹¹ Clonidine is often used in the perioperative setting in that it controls sympathetically driven hypertension while also providing an anesthetic and analgesic-sparing effect.¹²

Drug Differentiation and Mode of Delivery Considerations

All 5 drugs contained in the centrally acting medication class reduce BP similarly if equivalent doses are used. Clonidine and α -methyldopa are the only 2 drugs in this class, that are intravenously available. Clonidine is the only compound in this class that is offered in a transdermal delivery system.¹³ Onset and duration of action are features that distinguish compounds in this class. Clonidine has the quickest onset of action and, in most instances, the

shortest duration of effect. The half-life of drugs in this class widely varies and oftentimes has a weak correlation with the duration of effect.^{6,7}

α -Methyldopa

From the early 1960s to the late 1970s α -methyldopa remained a widely used drug in the treatment of all stages of hypertension.⁴ When used in doses ranging from 250 mg to 2.0 g/d, α -methyldopa effectively reduces supine BP without producing orthostatic hypotension. With the availability of newer, better tolerated antihypertensive medications, oral α -methyldopa has fallen out of favor beyond its use in pregnancy-induced hypertension and in patients with sympathetically driven forms of hypertension who are clonidine intolerant.¹⁴ Regarding the latter, α -methyldopa lacks fetal adverse effects in utero (maintains uterine perfusion, not teratogenic) and does not reduce maternal cardiac output, uterine, and/or renal blood flow.^{15,16} Methyldopa is offered in an intravenous formulation (as the parent drug ester) and is used in the case of hypertensive emergencies. The typical intravenous dose range for α -methyldopa is 20 to 40 mg/kg/d in divided doses every 6 hours. The treatment of hypertensive emergencies with intravenous α -methyldopa is dated, however, having been supplanted by more effective and easier-to-use compounds.

Clonidine

Oral clonidine has a rapid onset of action (30–60 minutes) and is of particular utility for managing hypertensive urgencies; however, it is comparatively short-acting and, in managing hypertensive urgencies, it commonly requires frequent dosing.¹⁷ A transdermal delivery system for clonidine is available and provides a constant daily amount of drug for 7 days. This delivery system takes 1 to 2 days to arrive at its peak effect. Blood levels of clonidine (and presumably its antihypertensive effect) linger for 8 to 24 hours following patch removal.¹⁸ Transdermal clonidine is best absorbed from a chest or upper arm location.¹⁹ Transdermal clonidine is of particular utility for the management of the labile hypertensive patient who requires multiple medications, the hospitalized patient who cannot take oral medications, and the patient with prominent early morning BP surges. At equivalent doses, transdermal clonidine is more likely than oral clonidine to be accompanied by dose-dependent salt and water retention.¹³

Guanabenz

Guanabenz is similar to clonidine in its mechanism of action but has a longer duration of

action. Guanabenz less commonly causes rebound hypertension, fluid retention, and/or orthostatic hypotension. It is not necessary to adjust the dose of guanabenz in patients with renal failure.²⁰ In contrast to clonidine, which undergoes significant renal elimination as the intact molecule, guanabenz is extensively biotransformed and should not accumulate in patients with severe renal insufficiency.

Therapy with guanabenz should generally begin at a dose of 4 mg twice daily, with increments as needed up to a maximum total daily dose of 64 mg. An interesting metabolic action of guanabenz is its ability to reduce total cholesterol levels by 10% to 20%. The presumed mechanism for this is an inhibition of hepatic cholesterol production and triglyceride synthesis, in addition to stimulation of fatty acid oxidation.²¹

Guanfacine

Guanfacine differs from the other members of this class in that its 24-hour duration of action typically allows it to be dosed once daily.²² Guanfacine appears to enter the brain more slowly and thereafter to persist in its antihypertensive effect longer than does guanabenz. Guanfacine is preferably dosed in the evening and, in so doing, its peak effect can be aligned with early morning catecholamine and BP surges. Evening dosing of guanfacine also allows any potential sedating effect to play out during sleep. As with other agents in this class, the BP-lowering effect of guanfacine is enhanced when combined with a diuretic. Guanfacine may be useful as an alternative to clonidine in patients intolerant to clonidine because of excessive sedation.²³ Finally, guanfacine has orphan drug status for the Fragile X syndrome (the most common inherited cause of mental retardation), as it relates to positively affecting the overarousability, impulsivity, and aggressiveness seen in this syndrome.

Moxonidine

Monotherapy or combination therapy with moxonidine effectively reduces BP.⁵ Moxonidine does not reduce heart rate as can happen with clonidine. The plasma half-life of moxonidine is only 2 to 3 hours; thus, its extended duration of action suggests prolonged binding to central imidazoline I₁ receptors. Moxonidine is extensively renally cleared, and its dose has to be adjusted according to the glomerular filtration rate (GFR).²⁴ The UK licensed prescribing information states that in patients with moderate renal impairment (GFR 30–60 mL/min), single doses of moxonidine should not exceed 0.2 mg and the daily dose should not go

beyond 0.4 mg; moxonidine should not be given in the setting of severe renal impairment (GFR <30 mL/min). Also, moxonidine use should be avoided in patients with advanced HF because a sustained-release form of moxonidine (force-titrated to 1.5 mg twice daily) was associated with an early increase in morbidity and mortality in a large cohort of New York Heart Association class II to IV (only 4% class IV) HF patients with an average pre-therapy ejection fraction of 25.9±6.5.²⁵

Rilmenidine

Numerous studies have established that oral rilmenidine (1–2 mg/d), alone or in combination with other antihypertensives, is effective and well-tolerated in the treatment of mild-to-moderate hypertension.⁶ A 1-mg daily dose appears to provide the most favorable ratio of efficacy to tolerability. Rilmenidine increases parasympathetic tone, which may account for its ability to not affect heart rate in the course of reducing BP.²⁶

BP-INDEPENDENT USES

Centrally acting agents and, in particular, clonidine, have a number of alternative uses beyond BP reduction. Clonidine may be used for migraine prophylaxis, post-traumatic stress syndrome, postmenopausal flushing, alcohol and opioid withdrawal symptoms, and to secondarily treat open-angle glaucoma. Clonidine has also been used effectively in various diarrheal states including that associated with the short-gut syndrome.²⁷ Clonidine has also been used in the perioperative period, as an adjuvant to general and/or regional anesthesia; to improve analgesia with systemic, spinal, or peripheral opioids; and to control postoperative sympathetic responses.¹³ As a result, anesthesia and analgesia requirement can be reduced. Of note, the sympatholytic effect of clonidine is primarily on tonic SNS activity and less so on reactivity. This is an important feature in the perioperative setting.

The sympathoinhibition that occurs with clonidine can enhance diuretic effect in cirrhotic patients with ascites and can reduce sympathetic hyperactivity, which is characteristic of HF.^{28,29} Oral clonidine can also control ventricular rate in new-onset atrial fibrillation with an efficacy not dissimilar to that of more traditional agents.³⁰ Clonidine can also be used in the diagnosis of pheochromocytoma. When 0.1 mg of clonidine is administered hourly for 3 doses, plasma norepinephrine levels decrease in patients with essential hypertension but go unchanged in patients with a pheochromocytoma.³¹

COMPLICATIONS

Class Side Effect Considerations

As with any antihypertensive agent that reduces SNS activity, postural hypotension, weakness, sodium and water retention, and gastrointestinal symptoms can arise relating to the adrenolytic action or the resultant override of parasympathetic function or both. Somnolence and dry mouth are the most common side effects with central sympatholytics and the major reason for discontinuation of any of these drugs.^{32,33} I₁-receptor stimulants are better tolerated in most instances and do not cause as much dry mouth and/or drowsiness.^{5,6}

Other central nervous system depressants such as sedative-hypnotics, benzodiazepines, antihistamines, and/or ethanol may exaggerate the sedative effects of drugs within this class. The dry mouth associated with centrally acting agents is a function of an α_2 -mediated reduction in salivary flow rate. This can be a very bothersome side effect that, if sufficiently long-lived, can increase the likelihood of dental caries, periodontal disease, and/or oral candidiasis.³⁴

Class Member-Specific Side Effect Considerations

Methyldopa. The intestinal absorption of α -methyldopa, and therefore its therapeutic effect, is reduced by concurrently ingested iron. Additional side effects with α -methyldopa include somnolence and depression, which may relate to a change in brain biogenic amines.^{32,33} Hypersensitivity reactions, including hepatitis and Coombs-positive hemolytic anemia (due to the appearance of an antibody with specificity for red cell Rh determinants) can occur with α -methyldopa. These reactions occur in 10% to 20% of patients receiving α -methyldopa (≥ 1 g/d) over several months.³⁵ α -Methyldopa can be continued in the presence of a positive direct Coombs test result alone; however, if anemia develops, therapy should be withdrawn. Drug-induced hepatitis with fever, eosinophilia, and increased transaminase values can occasionally develop with α -methyldopa. This is a self-limited process that remits with drug discontinuation. α -Methyldopa may also produce a flu-like syndrome marked by high fever (drug-induced). α -Methyldopa and its metabolic products can interfere with some assays for catecholamines and with the action of other therapeutic agents, such as levodopa, bromocriptine, and monoamine oxidase inhibitors.

Clonidine. Clonidine can suppress sinus and atrioventricular nodal function, which will sometimes result in significant bradycardia. Also, patients with

chronic kidney disease and sinus node dysfunction are at risk for developing significant bradycardia with clonidine, and this drug is best avoided in such individuals.³⁶ If clonidine is suddenly discontinued during treatment with high doses (usually >1.0 mg but sometimes lower doses), rebound hypertension may occur.³⁷ Rebound hypertension may be more prominent if β -blocker therapy is present when clonidine is discontinued. Such a rebound phenomenon has not been seen with moxonidine and rilmenidine.^{5,6}

Skin reactions to transdermal clonidine can include subjective signs of pruritus and objective findings such as erythema, hyperpigmentation/depigmentation, scaling, vesiculation, excoriation, and induration and occur in 15% to 20% of patients. Allergic dermatitis most commonly occurs in whites and women. Most studies have indicated that the skin reactions are related to the active drug and not patch components per se.¹³ Clonidine overdose can result in paradoxical hypertension if the vasodepressor effect of central α_2 -adrenergic stimulation is exceeded by the pressor effects of peripheral α_2 -adrenergic receptor stimulation.³⁸

Guanfacine. Tricyclic antidepressants, such as imipramine and amitriptyline, lessen the antihypertensive action of guanfacine (and clonidine) in that they are antagonists of the central α_2 receptors targeted by these compounds.

Guanabenz. The incidence of sedation in clinical trials with guanabenz is dose-dependent and ranges from 20% to 50%; however, guanabenz-related sedation appears to diminish over time in patients receiving maintenance treatment. Guanabenz has not been associated with weight gain and/or clinically apparent sodium retention.

Moxonidine/Rilmenidine. Monoamine oxidase inhibitors should not be coadministered with either of these compounds. Both compounds have fewer side effects than is the case for clonidine and α -methyldopa, which likely relates to a reduced affinity for α_2 receptors.^{5,6}

Side Effect Management

The side effects associated with centrally acting compounds can be most directly treated by discontinuation of the offending compound. There are sufficient patients for whom BP control is dependent on centrally acting agents, however, making medication discontinuation complicated. In such cases, several therapy options exist. Central-acting

compounds can be split-dosed such that the same total daily dose is given but at lower individual doses and more frequently. This approach has not been formally tested but empirically would seem to lessen the sedating effect of these compounds. In addition, nighttime dosing is an alternative, in which case the sedating effects of these medications can be exploited to facilitate sleeping; however, the decrease in salivary flow that accompanies these therapies (in particular, clonidine) can be quite discomfiting and may promote caries development.³⁴ If this occurs, salivary substitutes can be considered. Another treatment option is to lower the total daily dose of a centrally acting agent and direct therapy to alternative drug classes that are less liable to cause side effects. Also, within-class switches are sometimes of use; for example, a patient intolerant of the sedating effects of clonidine may be successfully switched to a less-sedating compound, such as guanfacine or guanabenz.

A final consideration with clonidine-intolerant patients is that they can be switched to the transdermal form of clonidine with which the side effects of sedation, fatigue, and/or dry mouth are fewer.¹³ Use of transdermal clonidine also lessens the risk of rebound hypertension with sudden discontinuation of therapy. Treatment with hydrocortisone cream or antacids (magnesium-aluminum hydroxide suspension) has been used to lessen the intensity of skin reactions to transdermal clonidine. Whether applied under or at the edges of the patch, 0.5% of hydrocortisone cream is occasionally effective in lessening the contact dermatitis; however, this has been poorly studied beyond the observation that pretreatment with hydrocortisone increases clonidine absorption and therefore plasma levels. The inconsistent response to hydrocortisone application may reflect the relative weakness of this compound as a corticosteroid. Alternatively, an aerosolized spray of the more potent corticosteroid beclomethasone may more favorably impact the skin sensitization seen with transdermal clonidine. The drying effect of the steroid spray will not affect patch adhesion to the skin surface, which has been viewed as a shortcoming of hydrocortisone cream.^{39–41}

SUMMARY

Centrally acting antihypertensive compounds remain an important therapy in the management of hypertension. A significant number of patients have their hypertension linked to the SNS so significantly that drugs in this class can be readily viewed as first-step therapies; however, centrally acting antihypertensive compounds are used most

regularly in an add-on capacity for general control of hypertension, whatever its primary origin. The prototype compounds in this class— α -methyldopa and clonidine—are now used less regularly because of a fairly oppressive side effect profile. There are several choices within the centrally acting antihypertensive medication class, however, which improves the chances of finding a well-tolerated compound. Centrally acting antihypertensive compounds are diversified in their actions, both reducing BP and favorably influencing a number of nonhypertensive circumstances coupled with SNS overactivity.

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