Clonidine

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Abbreviations

α	alpha
β	beta
BP	blood pressure
MSA	multiple system atrophy
OH	orthostatic hypotension
PAF	pure autonomic failure
PoTS	Postural Tachycardia Syndrome

Introduction

The conventional classification of PoTS in subtypes (hyperadrenergic, neuropathic and volume dysregulation) is based on clinical evaluation and review of symptoms but, as they are the final common pathway resulting from a number of different pathophysiologic mechanisms [1], they can overlap in the same patient, making pharmacological treatment complex.

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This chapter will focus on the use of Clonidine, a central sympatholytic, to improve BP control and alleviate symptoms in particular in 3 groups of patients:

- hyperadrenergic PoTS with increased BP
- patients with supine hypertension
- patients with severe neurogenic orthostatic hypotension (OH).

Clonidine: Mechanism of Action and Pharmacokinetics

Clonidine (2-((2,6-dichlorophenyl) amino)-2-imidazoline hydrochloride) is an Imidazoline derivative that acts as a central α-2 adrenergic agonist.

Anatomically, its site of action is the rostral ventrolateral medulla in the brainstem, whose afferents regulate vasomotor and chronotropic targets. Clonidine terminates the presynaptic release of norepinephrine and inhibits the sympathetic outflow. It can also reduce serum catecholamine levels [2]. Moreover, it increases the parasympathetic outflow from the medulla by preventing the action of cardio-inhibitory vagal neurons in the nucleus ambiguus.

Besides its central action it can act directly on peripheral pre-synaptic α-2 adrenergic receptors in the heart and vessels, thus preventing release of norepinephrine and local smooth vessel β-adrenergic activation.

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Altogether, treatment with Clonidine mediates increased vasodilation, reduced cardiac output and heart rate and reduced blood pressure.

As a centrally acting agent, Clonidine does not cause tolerance or reflex tachycardia. It is especially useful as fourth or fifth line antihypertensive drug, in patients with labile hypertension, significant BP variability and with a relevant component of anxiety. Oral Clonidine, at small doses, may be used in patients with symptomatic BP surges thanks to its short-lasting action. Other therapeutic indications include pain management, attention-deficit/hyperactivity disorder, and symptomatic treatment of opioid withdrawal, as adjuvant to induce sedation or for epidural analgesia.

Pharmacokinetics

Clonidine's pharmacokinetics differs according to the formulation prescribed.

For oral tablets the bioavailability varies between 75 and 100%. Peak plasma concentration is achieved in about 2 hours, with the maximal blood pressure reduction achieved between 3 and 8 hours. Clonidine is 20–40% protein bound in plasma. More than half of Clonidine is excreted unmodified in the urine and its half-life is between 6 and 24 hours.

The Clonidine transdermal adhesive system is a 0.2 mm thick patch composed of a drug reservoir, a membrane that controls delivery rate, and a pliable backing. Clonidine is released at a constant rate, with "zero-order" kinetics similar to continuous infusion. Clonidine patch formulations come in doses of 2.5, 5, and 7.5 mg contained in a timed matrix delivery system and deliver 0.1, 0.2, or 0.3 mg/day of Clonidine for 7 days, respectively. The elimination half-life while the patch is adherent varies from 26 to 55 hours.

Clonidine patches should be applied preferably on the chest or upper arms as these sites correspond to the higher average Clonidine concentration [3]. The amount released depends mainly on the contact surface area of the patch, especially in the early phases of treatment as the drug is sequestered in the stratum corneum.

Adverse Effects

As a central acting sympatholytic Clonidine also acts as a central nervous system depressant, causing or worsening fatigue, brain fog and drowsiness. It can also cause postural hypotension, sodium and water retention, and dry mouth. The spectrum of side effects makes the use of Clonidine in PoTS patients particularly challenging as they can overlap with symptoms associated to the syndrome including brain fog, fatigue, worsening of postural BP drop and of orthostatic intolerance. It is however possible to minimise this by starting with small doses and using a long-acting transdermal formulation.

Clonidine can act as a depressor of sinus and atrioventricular nodes and cause significant bradycardia, especially in patients with chronic kidney disease and sick sinus syndrome.

Sudden discontinuation of Clonidine, particularly when used at high doses and in association with β-blockers, can cause sympathetic surge with rebound hypertension. This is less common for the transdermal formulation, likely due to residual drug accumulation in the skin.

Besides these side effects secondary to its mechanism of action, it is important to recognise that transdermal Clonidine can cause additional skin reactions such as erythema, changes in skin color with hyperpigmentation or depigmentation, vesicular rash, excoriation, which may require treatment with corticosteroid creams.

Indication in PoTS/Dysautonomia

There are no randomized clinical trials on the use of Clonidine in PoTS, therefore most of the literature and also guidelines including the Heart Rhythm association Consensus on PoTS, Inappropriate Sinus Tachycardia and Vasovagal Syncope, mention the use of sympatholytic agents as supported by a class IIb Recommendation (level of Evidence E) [4].

We describe potential uses of Clonidine in the following settings.

Hyperadrenergic PoTS

The spectrum of symptoms of hyperadrenergic PoTS (palpitations, tachycardia, anxiety, orthostatic hypertension with BP raise ≥10 mmHg) and the finding of plasma norepinephrine levels ≥600 pmol/L after standing are suggestive of marked sympathetic activation, therefore the reduction in sympathetic outflow by Clonidine may be beneficial.

A study on a small group of patients with hyperadrenergic postural intolerance found that Clonidine improved symptoms and haemodynamic. As expected, it lowered blood pressure, heart rate, cardiac input but also raised peripheral vascular resistance and plasma norepinephrine levels on standing and improved plasma volume [5].

In our practice we would recommend to start with a small oral dose, and increase it up to 0.1–0.2 mg two to three times daily, or switch to a transdermal formulation if tolerated and when prolonged action is required or when patients are unable to tolerate oral administration.

Neuropathic PoTS—Peripheral Adrenergic Failure: Control of Supine Hypertension

Patients with neuropathic PoTS or with autonomic failure may present with supine hypertension, increased sympathetic activity being the shared pathophysiologic mechanism in these two types of orthostatic intolerances.

Nocturnal hypertension is associated with increased cardiovascular risk and target organ damage and requires treatment, which represents a challenge as these patients present with postural intolerance and, in case of autonomic failure, postural hypotension.

Shibao et al. tested Clonidine as an overnight medication in 23 patients with autonomic failure (either with MSA or with PAF) and observed significant reduction of supine BP and reduction in nocturnal natriuresis compared to placebo [6]. The BP effect was observed in both subgroups although the mechanism underlying supine hypertension is believed to be different-residual sympathetic tone unrestrained by the lack of baroreflex buffering in MSA and damage to postganglionic sympathetic neurons in PAF.

Treatment of Severe Hypotension in PoTS: Use as a Pressor Agent

While Clonidine lowers blood pressure in patients with essential hypertension, it can "paradoxically" raise blood pressure in patients with autonomic failure or PoTS, by acting as an agonist of peripheral post-junctional α_2- and α_1-adrenergic receptors in the venous bed. This novel use for clonidine was described by Robertson et al. who analyzed the pressor response of patients with idiopathic orthostatic hypotension to oral Clonidine and found that BP was significantly raised for several hours with durable improvement of symptoms [7].

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