Review Article

Indian Journal of Anesthesia and Analgesia
2019; 6(6) (Part - I): 2057-2062
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6619.30

Clonidine a Wonder Drug

Ashwani Sharma[1], Lalit Gupta[2]

[1]Senior Resident, [2]Associate Professor, Department of Anaesthesia and Critical Care, Maulana Azad Medical College and Lok Nayak Hospital, Bahadur Shah Zafar Marg, New Delhi 110002, India.

Abstract

Background and Aims: The alpha-2-adrenergic agonist drugs are now widely used in anesthesiology for multiple purposes and are not limited only to intraoperative and postoperative analgesia. Clonidine, an imidazoline derivative belongs to this class and has selectivity ratio of 200:1 for alpha-2: alpha-1 receptors. *Contents:* Apart from its antihypertensive and anti-adrenergic effects, recent studies have established clonidine as a wonder drug to be an effective analgesic, sedative and has an opioid sparing effect with decreased anesthetic requirements intraoperatively. Therefore, a detailed analysis and discussion for possible new role of clonidine in anesthetic armamentarium seems to be need of the hour. This review highlights pharmacological aspects, mechanisms of action, opioid sparing effect, potential indications and adverse effects. *Conclusion:* Although Clonidine reduces post-operative pain intensity and nausea apart from some other uses like alcohol withdrawal, acute hypertension, smoking cessation, cancer pain management and adjuvant to local anesthetics. However, one should be vigilant while using it for high risk of perioperative low blood pressure and bradycardia.

Keywords: Clonidine; α2 adrenoceptor agonist, Antihypertensive.

How to cite this article:

Ashwani Sharma, Lalit Gupta. Clonidine a Wonder Drug. Indian J Anesth Analg. 2019;6(6 Part -I):2057-2062.

Introduction

Clonidine is an α2 adrenoceptor agonist. It carries central sympatholytic action. Clonidine shows reduction in peri-operative hemodynamic instability and enhances the effect of anesthesia. Clonidine reduces sympathetic outflow by acting on central nervous system. Clonidine hydrochloride is an imidazoline derivative. It was synthesized in 1960 and was used clinically as nasal decongestant attributed to its α1 agonist mediated vasoconstrictor action. Antihypertensive action of clonidine is derived from its α2 agonist property. In 1966, it was first used in Europe in clinical context and later in United States as antihypertensive and since, than its prevailed worldwide.

Contents

Pharmacology

Clonidine is chemically 2 [(2, 6 Dichlorophenyl) Imino] Imidazoline Mono hydrochloride. Clonidine is a derivative of well-known α sympathomimetic drugs naphazoline and tolazoline. It was develoved in early 60s. It was synthesized originally as a nasal vasoconstrictor. In its clinical trials it was found to cause hypotension, bradycardia, and sedation. In 1966, in Europe it was first introduced as an antihypertensive and then later in United States of America. It was the first-known antihypertensive to act on central nervous system.

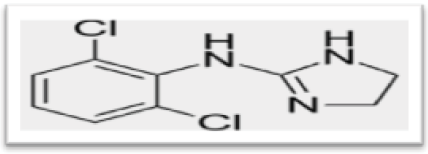

Fig. 1: Clonidine is chemically C9H9Cl2N3. HCL

Mechanism of Action[1,2]

Clonidine is selective α-2 agonist. It has selectivity ratio of 200:1 for α-2: α-1 receptors. It acts on

Corresponding Author: Lalit Gupta, Associate Professor, Department of Anaesthesia and Critical Care, Maulana Azad Medical College and Lok Nayak Hospital, Bahadur Shah Zafar Marg, New Delhi 110002, India.

E-mail: lalit.doc@gmail.com

Received on 01.08.2019, **Accepted on** 04.09.2019

imidazoline receptors I1 and I2 with a higher selectivity for I1 receptors. Its action comes from modulation of inhibition of noradrenaline release by acting on presynaptic imidazoline receptors. Clonidine produces wide variety of its actions by acting on these receptors, the receptor distribution on the target organs, clonidine selectivity to bind, and type of endogenous ligand activated.

Pharmacokinetics

Clonidine is almost completely absorbed from gastrointestinal tract. Its absorption is very rapid. Its bioavailability is nearly 100 percent. Onset of action starts within *30* to *60 minutes* after oral intake. Peak plasma concentration reaches with *90 minutes*. The elimination half life is 6 to 24 with a mean of *12 hours*. Routes of administration are oral, parentral, intra-muscular, intra-venous, transdermal, nebulization, extradural, and intrathecal routes. Rectal administration is known in children also. It is well absorbed through skin because of its low molecular weight and high lipid solubility. After transdermal clonidine patch implantation, stable plasma concentrations are reached after *2–3 days*. The fluctuation in plasma concentration is very less. Clonidine is distributed throughout the body, the highest concentration being in organs of elimination *i.e*., kidney, gut and liver. The brain concentrations are low but higher than plasma concentrations. Clonidine is metabolized mainly by the liver to produce Hydroxyclonidine which subsequently undergoes glucuronidations to produce O-glucuronide and is excreted in urine. 40 to 60% of an orally administered dose is excreted unchanged in urine within *24 hours*. In presence of renal insufficiency, renal clearance is markedly reduced and 95% of clonidine administered is excreted in urine and faeces in *72 hours* and complete clearance occurs in *5 days*. Clonidine given as an adjuvant in local anesthesia for epidural infusion accts by three different mechanism of action:

1. α2 receptors in dorsal horn stimulation decreases the pain transmission;
2. Local vasoconstriction caused by clonidine decreases absorption of local anesthetic agent;
3. Clonidine stimulates production of neuraxial opioids and it produces additive effects along with fentanyl.

Dosage

Clonidine has been used in a wide dose range for various studies. The clinically effective range is *2* to *7 μg/kg* body weight.

Pharmacological Effects

1. *Cardiovascular System:*[3] The actions are classified as peripheral and central.

   Effects on heart: Clonidine inhibits norepinephrine release from the peripheral prejunctional nerve endings and causes bradycardia. There are no postjunctional α-2 receptors in myocardium. Hence a direct effect on heart is unlikely. It causes hypotension due to centrally mediated reduction in sympathetic outflow. Clonidine exerts vagomimetic effect on heart by stimulating nucleus tractussolitarius which can be attenuated completely by highly selective muscarinic M2 receptor antagonists. It can cause bradycardia and reduction in cardiac output without affecting the cardiac contractility and peripheral vascular resistance. It enhances the baroreflex sensitivity. In higher doses it depresses the atrioventricular nodal conduction with slight prolongation of P-R interval. It has antiarrhythmic action mediated via imidazoline receptors and vagus.

- Effects on Coronary Vessels:[4] *In vivo*, clonidine causes coronary vasodilatation by releasing Endothelium Derived Relaxing Factor (EDRF). It also enhances the vasodilatation caused by endogenous and exogenous adenosine. The vasoconstrictive action on proximal coronary bed is due to predominance of α-2 adreno receptors causing direct vasoconstriction. This effect is offset by the central reduction in sympathetic outflow.
- Effect on Hemodynamics;[5] Clonidine potently inhibits the firing rate of locus coerulus which mediates the normal response, and exerts its hypotensive action by a net reduction in Central Sympathetic Outflow. The α-2 agonists hyperpolarize and depress the locus cerulus through potassium channels and markedly reduce the noradrenaline concentration. The studies on receptor binding have stressed that imidazoline I_1 receptors in ventrolateral medulla are responsible for mediating the blood pressure reduction. By its action on post junctional α-2 and α-1 adrenoreceptors in vascular smooth muscle it causes vasoconstriction. This activation is a result of influx of extracellular calcium and could be blocked by α-2 antagonists or the dihydropyridine calcium channel blocker,

nifedepine. It causes vasodilatation by its release of Endothelium Derived Relaxation Factor (EDRF). Bradycardia caused by α-2 adrenergic agonist clonidine has been attributed to either increased baroreflex sensitivity,[6] stimulation of nucleus tractus solitarius causing vagomimetic effect, or depression of AV conduction.

2. *Central Nervous System:* Clonidine causes dose related sedation, EEG confirmed increase in stage I and stage II sleep with a decrease in rapid eye movement sleep. In small doses it causes anxiolysis[7] almost comparable to that seen with benzodiazepines. It has biphasic effect, being anxiolytic in small doses with α-2 stimulation and anxiogenic in higher concentrations through α-1 action. This effect is lost with chronicity of administration. It has a powerful analgesic action both at supraspinal and spinal levels. Its potency is enhanced synergistically by opioids, acting through independent receptors.[8] Clonidine, by its action on α-2 rece=ptors reduces the anesthetic requirements. It reduces the minimum alveolar concentration of Halothane and Isoflurane.[9] This action is not limited to volatile anesthetics. It also causes a reduction in the required dose of induction agents. Clonidine reduces the cerebral blood flow, in subjects anesthetised with Halothane or Isoflurane and blunts the cerebrovascular response to hypoxia. It reduces intracranial pressure and cerebral metabolic oxygen requirement.
3. *Respiratory System:* Clonidine has minimal respiratory depressant effect, much less compared to that of opioids. In clinical dose settings it is rarely encountered. It does not potentiate the respiratory depression caused by opioids,[10] Nebulised clonidine attenuates the bronchoconstriction produced by histamine in asthmatics and also is used in patients with obstructive sleep apnea syndrome.
4. *Gastro Intestinal System:* Clonidine has a prominent antisialagogue effect with a direct action. While activation of prejunctional α-2 adrenoreceptors inhibit the vagally mediated release of gastric acid from parietal cells and also reduces gastric motility. It does not alter the gastric pH significantly[11]. Clonidine reduces the secretion of water and electrolytes from large bowel.
5. *Renal System:* Clonidine causes diuresis. The possible mechanisms are inhibition of Anti-diuretic Hormone (ADH) release, decrease in vasopressin level, blockade of action of ADH on renal tubules, increase in glomerular filtration rate. Other possible mechanisms are release of atrial natriuretic peptide and an α-2 action on juxta glomerular apparatus.
6. *Neuroendocrine System:* Clonidine inhibits the centrally mediated sympathicoadrenal outflow as seen by the decreased levels of catecholamines in circulation and decreased level of their metabolites in urine. It enhances the release of growth hormone by its action post-synaptically on the hypophyseal cells. It can inhibit steroidogenesis, by virtue of the imidazole ring in its molecule. It inhibits ACTH release from pituitary, thus preventing the rise in Cortisol level as a consequence of surgical stimulation. Clonidine directly acting on beta cells of Islet of Langerhans inhibits insulin secretion. This does not cause significant hyperglycemia and is short lived. It is known to inhibit lipolysis in adipose tissues. Clonidine reduces the plasma renin activity, as a result of decreased sympathetic activity or direct inhibition of renin release. It also suppresses aldosterone production. There are no demonstrable effects on glucose tolerance and potassium balance.
7. *Hematologic System:* It produces platelet aggregation *in vivo*. This effect is clinically not seen because the norepinephrine levels required for the aggregation are not achieved *in vitro*.
8. *Reproductive System:* The α-2 adrenoreceptorare found post-synaptically in myometrium, which may mediate uterine relaxation. This effect of clonidine is largely undefined.
9. *Effects on Lipids:* Clonidine has been reported to reduce the atherogenic low-density lipoprotein without affecting the cardio protective high-density lipoprotein. The net result is a decrease in LDL/HDL ratio thus decreasing the cardiovascular risk.

Adverse Effects

There are no known contraindications to clonidine therapy other than known hypersensitivity. The most commonly seen adverse effects are dry mouth, drowsiness, hypertension and bradycardia, if large doses are used. Withdrawal phenomenon is reported after chronic clonidine treatment and sudden withdrawal. There is no evidence of sympathetic over activity after single dose therapy.

It probably takes up to *six days* of continuous therapy to produce adaptive changes. In single dose peri-anesthetic therapy such rebound phenomena are not seen. And the hypertensive rebound when occurs is effectively treated with Labetolol. Sudden withdrawl of clonidine should be avoided otherwise rebound hypertension and withdrawl symptoms will occur. Dose titration should be done in renal impairment, severe coronary artery disease, bradycardia, hypotensive patients. It should not be given above C4 dermatome in epidural infusion.

Alpha-2 Antagonists: Potent, selective and specific α-2 antagonists such as Idazoxan and antipamezole have been developed. The α-2: α-1 selectivity ratio of antipamezole is 200 times higher than Idazoxan.

Common side effects

Hypotention; Nausea; Vomiting; Drowsiness; Headache; Fatigue; Dizziness; Abdominal pain; Emotional instability; Sedation; Sexual dysfunction; Xerostomia; Constipation.

Serious side effects

Bradycardia; Syncope; Severe hypotension; Severe allergic reaction; Angioedema; A-V block; Depression;

Use in Parturients: It is not advised to use epidural clonidine in parturients because of the risk of development of severe hypotension and bradycardia;

Clonidine addiction: Clonidine has a potential to be used as a habit forming drug, and it can be used as a potential substance of abuse. It should be monitored while prescribing this drug.

Physiology [1,12,13]

Receptor Classification:[12]

Adrenoreceptors

A. Classification: Ahlquist R P (1943) differentiated adrenergic receptors into α and *beta* based on responses of various amines in different physiological preparations. The next advancement was the finding that there are sub-classes of receptors at pre-synaptic nerve endings which regulate the release of neurotransmitter. This led to sub-classification of *a* adrenoreceptors based on their synaptic locations into post-synaptic α-1 and pre-synaptic α2. These were further confirmed by the use of newly developed α adrenoreceptor agonists and antagonists. This sub-classification was pharmacologically supported using specific antagonists like prazosin, a potent α-1 antagonist and yohimbine, a potent α-2 antagonist.

B. Physiology: The transmembrane signalling for the α-2 adrenergic responses involve the combination of three separate components:

1. Receptor Protein: A-2 adrenoreceptor is a G-Protein membrane receptor consisting of 415–480 amino acids, which are arranged in a fashion forming α helical embedded in cell membrane. This transmembrane protein is responsible for binding with ligands.

2. G Proteins: All α sub-units have a single high affinity binding site for guanine nucleotide, have intrinsic GTPase activity and are substrate for ADP ribosylation.

3. Effector Mechanism: There are at least five separate effector mechanisms that are modulated by activated *a-2 adrenoreceptors*. Any one receptor may couple with more than one effector mechanisms.

The effector mechanisms are:

(i) Inhibition of Adenylate Cyclase: Causing a fall in cyclic AMP level. This results in cAMP dependent protein kinase activity and decrease phosphorylation, which alters biologic response.

(ii) Acceleration of Na+/H+ exchange: Activation of α-2 adrenoreceptor accelerates *Na+/H+* exchange which in turn stimulates phospholipase A2 to initiate the arachidonic acid breakdown pathway leading to release of thromboxane A2.

(iii) Activation of potassium channels: The G-protein mediated efflux of potassium channels hyperpolarize the membrane and thus suppress neuronal firing.

(iv) Inhibition of voltage sensitive calcium channels: The α-2 adrenoreceptors mediated blockade of calcium++ channel suppresses the calcium ++ entry into the nerve terminals and blocks the fusion of transmitter containing vesicles with synaptic membrane.

(v) Modulation of phosphatidyl inositol turnover: This turnover mediated by phospholipase C, in certain circumstances is modulated by α-2 adreno receptor activity.

Imidazoline Receptors

The first evidence for different sites of action of

clonidine was proposed by Bousequet *et al*. Later it was found that Ventrolateral Medulla (VLM) in the cervical region was an important connecting component of the baroreceptor reflex. The Ventrolateral Medulla contains both imidazoline and α-2 receptor binding sites. Ernsberger confirmed this observation and classified the imidazoline receptors into Imidazoline receptor I_1 and I_2 based on pharmacological studies.

Physiology: The functional receptor binding studies have shown that it was almost exclusively the I_1 receptor and not α-2 adrenoreceptor responsible for mediating the blood pressure reduction. The application of idazoxan which is I_2 receptor antagonist can blunt the effects of clonidine induced at ventrolateral Medulla, while the α2 antagonists that do not have imidazolinemoities are devoid of this property. The different imidazoline compounds with α-2 agonist activities have different selectivity for I_1 and α-2 adrenoreceptors. Clonidine has *3.8 times* higher selectivity for I_1 than α-2 adrenoreceptors. This selectivity is the factor that mediates blood pressure reduction in the ventrolateral medulla, while α-2 adrenoreceptors mediate expression of drowsiness and dry mouth, typical side effects of clonidine therapy, The chromaffin cells of the adrenal medulla[14] almost exclusively possess imidazoline receptors. A protein molecule has been isolated from these cells of adrenal medulla that shows specific binding sites for imidazolines but not for α-2 adrenoreceptor ligands.

The endogenous ligand for this α-2 adrenoreceptor has been discovered, isolated from calf brain, called as Clonidine Displacing Substance (CDS) in 1984. It has a molecular weight of 500, and could displace clonidine, yohimbine from α-2 adrenoreceptors. Clonidine Displacing Substance is the naturally occurring agonist for imidazoline receptors. A structural similarity to a certain extent exists between α-2 and imidazoline receptors because guanidine possesses a high affinity for both these types of receptors. Therefore, an anti-hypertensive effect mediated via I_1 receptors in distinction to an action at α-2 receptor should result in hypotension with less centrally mediated side effects.This understanding of receptor sub-types helps to achieve the desired effect[15] by activation of specific receptors and its complete reversal by selective antagonists

Clonidine uses and dosages

1. Tablet (extended release):
   - Dosages: *100 mcg;*
   - Use: Alcohol withdrawal, attention deficit hyperactive disorder, smoking cessation, menopausal flushing, restless leg syndrome, Tourette syndrome, post-therapeutic neuralgia, dysmenorroea and psychosis.
2. Tablet (fast release):
   - Dosages: *100 mcg, 200 mcg, 300 mcg;*
   - Uses: Opioid withdrawal, pheochromocytoma, acute hypertension and hypertension.
3. Transdermal patch (extended release):
   - Dosages: *100 mcg/day, 200 mcg/day, 300 mcg/day*, patch should be changed every 7^{th} day;
   - Uses: Opioid withdrawal, hypertension, menopausal flushing, smoking cessation, hypertension and cyclosporine nephrotoxicity.
4. Injectable
   - Dosages: *100 mcg/ml, 500 mcg/ml;*
   - Uses: Can be used for epidural infusion in case of cancer pain management and it can be used as an aduvent in local anesthesia;
   - Epidural dose is *30 mcg/hr* as initial dose and then titrated as per pain score and side effects.

Dosages need to be titrated in cases of renal impairment and to be started with a low dose.

Future prospects

Clonidine has been approved by FDA for treatment of attention deficit hyperactive disease children in 2010, Tics associated with Tourette syndrome, and severe pain related to cancer[16] has a treatment option with clonidine. Management of withdrawal symptoms associated with opioids, benzodiazepines,alcohol and treatment of insomnia, anxiety and post-traumatic stress disorder are some of the off label uses of clonidine.

Clonidine suppression test:[17] Catecholamine levels are measured before and after giving oral dose of clonidine in pheochroma patients. In normal healthy people there should be decrease in the level of catecholamines in circulation because of the effect of clonidine on sympathetic nervous sytem it decreases the level of epinephrine in circulation.

Conclusion

Clonidine can be given as pre-medication or adjuvant with local anesthesia to the patients posted for surgery. It provides added advantage of reduction in post-operative complications like nausea, shivering, hypertension. Peri-operative requirement of anesthetic agents are evident to reduced. Better pain management both intra-op and post-operatively, its easy and effective administration, hemodynamic stability with reduction in post-op analgesic requirments makes it a future proof drug to be used in anesthesia. Management of severe pain in cancer patients makes it indispensable in medical field. Epidural clonidine makes it a better choice for increasing the duration of motor blockade, decreasing intra-operative and post-operative pain.[18,19] Hypotension and bradycardia should be taken care of while giving systemic or by epidural route.

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