CLONIDINE

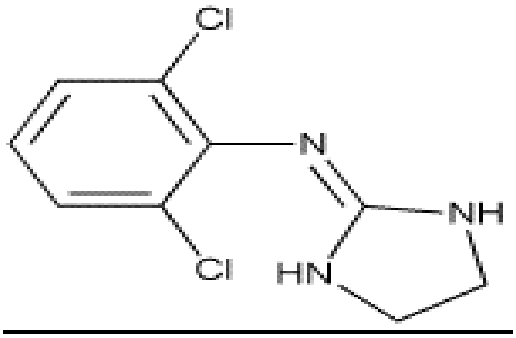
Clonidine, is a centrally selective partial $\propto_2$ adrenergic agonist that acts as an antihypertensive drug by virture of its ability to decrease sympathetic nervous system output from the central nervous system.

The first report of use of $\propto_2$ –adrenergic agonist clonidine, in human appeared in 1988 (Glynn et all)

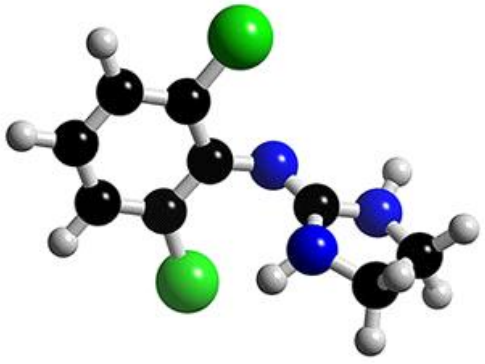
SYSTEMATIC (IUPACS) NAME :

N-(2,6-dichlorophenyl) –4,5 – dihydro-1 H-Imidazol – 2 – amine

STRUCTURE:



3D MODEL OF CLONIDINE



CHEMICAL DATA : ***FORMULA :*** $C_9H_9CL_2N_3$

MOL MASS : 230.093g/mol

Clonidine, is a centrally acting $\propto_2$ agonist hypotensive agent. It is an imidazoline derivative and exists as a mesomeric compound.

Clonidine hydrochloride is an odorless, bitter, white, crystalline substance soluble in water and alcohol. When administered,clonidine is transported by lipids by bonding to albumin. About 50% of the oral dose is metabolised by minor pathways in the liver. It is excreted by the kidneys.

MECHANISM OF ACTION:

These $\propto_2$ adrenergic agonists produce clinical effects by binding to $\propto_2$ receptors, there are 3 subtypes of $\propto$ receptor -$\propto_{2A}$, $\propto_{2B}$ and $\propto_{2c}$. Each is responsible for some but not all of the actions of $\propto_2$ agonists.

$\propto_{2A}$ - Mediate sedation, analgesia, sympatholysis

$\propto_{2B}$ - Mediate vasoconstriction, antishivering effects.

$\propto_{2C}$ – Mediate startle response.

Highest density of $\propto_2$ is present in the pontine locus ceruleus. It is important source of sympathetic nervous system innervations of the forebrain and a vital modulator of vigilance. Sedation is due to inhibition of this nucleus. Clonidine stimulates $\propto_2$ adrenergic inhibitory neurons in the medullary centre.

↓ Sympathetic outflow from CNS to peripheral tissues

↓ Sympathetic outflow causes ↓ Bp, ↓Heart rate, ↓ cardiac output,

↓ Diastolic pressure is more significant than systolic pressure.

Renal blood flow and glomerular filtration rate remain essentially unchanged. Normal postural reflexes are intact; therefore, orthostatic symptoms are mild and infrequent. Clonidine modifies k^+ channels in CNS therefore decrease the dose of anesthetics, $\propto_2$ adrenergic agonists – clonidine inhibits release of norepinephrine.

On spinal cord, activation of postsynaptic $\propto_2$ receptors in the substantia gelatinosa in spiral cord produces analgesia. Neuraxial placement of clonidine inhibits spinal substance P release and nociceptive neuron firing produced by noxious stimulation. Sedation produced by clonidine produces a calm patient who can be easily aroused to full consciousness. These drugs which activate GABA receptors produce clouding of consciousness, eg. Thiopentone and propofol ,tolerance and dependence.

PHARMACOKINETICS :

Clonidine is readily absorbed after oral administration.

Reaches peak concentration in 60 to 90 minutes. Elimination half time is in 9-12 hours.50% is metabolised in the liver, rest is excreted as it is in the urine. It is excreted in the urine as unchanged drug and metabolites, 40 to 60% of an oral dose being excreted in 24hrs as unchanged drug ; about 20% of a dose is excreted in the faeces, probably via enterohepatic circulation.

Clonidine is absorbed through the skin; absorption is reported to be better when applied to the chest or arm than when applied to the thigh. Therapeutic plasma concentrations are achieved in 2 to 3 days after application of a transdermal delivery system and are roughly equivalent to concentrations achieved after oral dosage therapeutic plasma

concentrations are maintained for about 8hrs after removal of the delivery system and then decline slowly over several days.

ROUTES OF ADMINISTRATION :

1. Oral tablets.
2. Transdermal patches.
3. Combination tablets (Clonidine + chlorthalidone).
4. Intrathecal / epidural injection, intravenous.
5. IVRA.
6. Plexus block.

DOSAGE :

CLONIDINE DOSAGE FORMS

Formulations	**Trade Name**	**Available dosage Strength**
Oral tablets	Clonidine tablets (generic available)	0.1, 0.2 and 0.3mg
Transdermal patches	Clonidine – TTS(catapress)	0.1, 0.2 and 0.3 G/3mg/24hrs
Combination tablets	Clonidine and chlothalidone	0.1 mg clonidine/15mg chlorthalidone 0.2 mg clonidine/15mg chlorthalidone 0.3 mg clonidine / 15mg chlorthalidone
Injection	Cloneon,Duraclon	500mcg/ml, 100g/ml as 10ml vials. 150mcg/ml

ADVERSE EFFECTS

Most adverse effects are mild and tend to diminish with continued therapy.The most frequent are dry mouth, occuring in about 40 of 100pts; drowsiness about 33 in 100; dizziness about 16 in 100; constipation and sedation, each about 10 in 100, other adverse effects include;

BODY AS WHOLE:

Weakness 10 in 100 pts; fatigue, headache and withdrawal syndrome.

CARDIOVASCULAR:

Orthostatic hypotension, about 3 in 100 pts, palpitations, tachycardia and bradycardia, including sinus bradycardia with atrioventricular block, other ECG disturbances, heart failure, hallucinations, cramp, Raynaud's syndrome.

CENTRAL NERVOUS SYSTEM :

Nervousness and agitation, about 3 in 100pts, mental depression and insomnia about 5 in 100, other behavioral changes are, vivid dreams or night mares, restlessness, anxiety, visual and auditory hallucinations and delirium have rarely been reported.

DERMATOLOGICAL :

Rashes, about in 100pts, pruritis about 7 in 1000 pts,angioneurotic edema and urticaria 5 in 1000pts, alopecia about 2 in 1000.

GASTROINTESTINAL :

Dryness of mouth – xerostomia most common side effect. Nausea and vomiting about 5 in 100pts, anorexia and malaise, each 1 in 100; mild transient abnormalities in liver function tests, hepatitis, parotitis, constipation, pseudo-obstruction and abdominal pain rarely.

GENITOURINARY:

Decreased sexual activity, impotence and loss of libido, about 3 in 100 patients, nocturia 1 in 100, difficulty in maturation about 2 in 1000, urinary retention about 1 in 1000.

HAEMATOLOGICAL :

Thrombocytopenia, rarely.

METABOLIC :

Weight gain, about 1 in 100pts, gynaecomastia 1 in 100; transient elevation of blood glucose / serum creatinine phosphokinase.

MUSCULOSKELETAL:

Muscle /Joint pain, about 6 in 1000, leg cramps 3 in 1000.

ORO-OTOLARYNGEAL :

Dryness of nasal mucosa.

OPHTHALMOLOGICAL :

Dryness of eyes, burning of the eyes and blurred vision were reported.

OVERDOSE :

Hypertension may develop early and may be followed by hypotension, bradycardia, respiratory depression, hypothermia, drowsiness, decreased or absent reflexes, weakness, irritability, and miosis. The frequency of CNS depression may be higher in children than in adults. Large overdose may result in reversible cardiac conduction defects or dysrhythmias, apnea, coma and seizures. Signs and symptoms of overdose generally occur 30min to 2hrs after exposure.

Management

There is no specific antidote for clonidine overdosage, clonidine overdosage may result in the rapid development of CNS depression; therefore, induction of vomiting with Ipecac syrup is not recommended. Gastric lavage may be indicated following recent and /or large ingestions. Supportive case may includes atropine sulfate for bradycardia, intravenous fluids and/or vasopressor agents for hypotension and vasodilators for hypertension.

Naloxone may be useful adjust for the management of clonidine induced respiratory depression, hypotension and /or coma; blood pressure monitoring to be done as naloxone has occasionally resulted in paradoxical hypertension.

WITHDRAWAL :

Patients should be instructed not to discontinue therapy without consulting their physician.Sudden cessation of clonidine treatment has, in some cases, resulted in symptoms. such as nervousness, agitation, headache and tremor, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma. Rare instances of hypertensive encephalopathy, cerebrovascular accidents and death have been reported.

INTERACTIONS :-

Drug	***Possible Effects upon Clonidine***	***Precautions***.
CNS depressants (Opiates, analgesics Sedatives)	Additive	Monitor for additive CNS effects

Tricyclic antidepressants (imipramine, desipramine)	Block hypotensive effect	Monitor blood pressure response
Hypotensive agents (diuretics)	Enhance hypotensive effect	Should be used with caution
Beta- blockers	Rebound hypertension with abrupt clonidine withdrawal	Monitor for hypertensive response, withdraw beta-blockers before withdrawing clonidine or slowly taper clonidine over 1 to 2 wks.
Cardiac glycosides	Enhanced bradycardia	Observe
Local anesthetics	Prolong the duration of effects of epidural local anesthetics	Observe

CLINICAL UTLITY OF CLONIDINE

- **Cardiovascular /circulatory**
    1. Hypertension
    2. Hypertensive emergency
    3. Atrial fibrillation
    4. CCF
    5. Orthostatic hypotension

- **Analgesia**
    1. Intraoperative and postoperative pain
    2. Subarachnoid and epidural analgesia
    3. Paediatric caudal anaestheia.
    4. Intractable Cancer pain
    5. Cluster headache proplylaxis
    6. Chronic headache
    7. Migraine headache
    8. Labor analgesia

- **Neurology**
    1. Peripheral neuropathy
    2. Neuropathic orofacial pain
    3. Diabetic gastroparesis
    4. Post epidural shivering
    5. Restless leg syndrome
    6. Hypertonicity
    7. Tetanus – induced autonomic dysfunction
    8. Tourette's syndrome.

- **psychology**
    1. Substance withdrawal
    2. Acute anorexia nervosa
    3. Attention – deficit / hyper activity disorders.
    4. Bipolar disorder
    5. Narcolepsy
    6. Panic disorder

- **Gastro intestinal**
    1. Carcinoid associated diarrhoea
    2. Ulcerative colitis and proctitis

- **Anaesthesia/Sedation/ Sergery**
    1. Antiemetic in children
    2. Maintaence of stable haemodynamics
    3. Laryngoscopy
    4. Liver transplantation
    5. Rhinoplasty

- **Endocrinology**
    1. Hyperthyroidism
    2. Treatment of growth delay

- **Miscellaneous**
    1. Excessive sweating
    2. Hot flushes
    3. Prevention of cyclosporin –induced nephrotoxicity

USES

PREANAESTHETIC MEDICATION

Oral clonidine 5ug kg^{-1} blunts cardiovascular response to laryngoscopy, intubation.

↓ Bradycardia,

↓ BP

↓ Plasma catecholamine concentration

↓ Inhaled anaesthetics, IV anaesthetics

Blunts cardiovascular response to ketamine, desflurane.

CENTRINEURAXIAL BLOCK :

It prolongs sensory and motor blockade of local anaesthetics. Duration of brachial plexus block is also prolonged.

Protection against myocardial ischemia

Clonidine decrease myocardial ischemia, infarction and mortality, following cardiovascular surgery. This is superior to beta-blocker.

DIAGNOSIS OF PHEOCHROMOCYTOMA

Clonidine 0.3mg orally decrease plasma concentration of catecholamines in normal patients but not in pheochromocytoma.This is because clonidine suppresses indogenous release of catecholamines from nerve endings but not diffusion of excess of catecholamines into circulation from pheochromocytoma.

TREATMENT OF OPIOID AND ALCOHOL WITHDRAWAL SYNDORME

10µg kg^{-1} of clonidine decreases sympathetic response with cardiovascular stimulation and attenuates increases in plasma concentration of catecholamine with naloxone administration is patients addicted to narcotics during general anesthesia.

Clonidine prevents withdrawal syndrome of alcoholic abusers.

TREATMENT OF SHIVERING

Clonidine inhibits thermoregulatory control, decreases vasoconstriction and shivering thresholds.

CONTRAINDICATIONS

Clonidine should not be given to patients with hypertension

CONCLUSION

Clonidine from the time of introduction in 1988 has been clinically used in a number of situations. It offers a useful and efficient solution to a number of anesthetic problems.

It has been implicated in anesthetic management as it is advantages in many ways.

- Mainly stabilize the cardiovascular response to the stressful condition (laryngoscopy, intubation)
- Reduce the dose of anesthetic drugs & prevents the harmful sideeffects of anesthetic drug.
- Reduce the hypertension & hypertensive crisis
- Prolongs the duration of action of intrathecally injected drugs
- Used in pain management both acute and chronic.

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