# Clonidine and Anaesthesia

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## KEY POINTS

- Clonidine is an α-2 adrenoceptor partial agonist with a growing significant role in clinical anaesthesia and perioperative medicine.
- Clonidine has been shown to be effective in reducing anaesthetic agent requirement and postoperative opioid requirement.
- Clonidine is a versatile drug that can be used in the critical care setting for sedation.
- Clonidine can be used as an effective adjunct to local anaesthetics to prolong their action and provide analgesia.
- Clonidine has a unique role in managing opioid-induced hyperalgesia, symptoms of alcohol withdrawal, and postoperative shivering.

## INTRODUCTION

Clonidine was first synthesised in the 1960s as an antihypertensive agent and has since found a variety of clinical uses. It was first used in human anaesthetic practice in 1984, where it was administered epidurally, and it remains in use primarily for its anaesthetic-sparing and sedative properties. In the United Kingdom, it is commonly used as part of a multimodal approach to analgesia and for its sympatholilytic properties. Unlike some other sedative agents, clonidine does not appear to induce respiratory depression, but its use is often limited by cardiovascular side effects. In this article, we will look at the science and pharmacology of the drug and then at its clinical uses in detail.

## PHARMACOLOGY

Clonidine is a heterocyclic imidazoline compound with a molecular weight of 266.56, which demonstrates agonism at the alpha-adrenergic class of receptors. It has a 200-fold greater affinity for α-2 than for α-1 receptors, and although its effects at the α-2 receptor predominate, under some circumstances its activity at α-1 receptors can manifest clinically.[1] The α-2 receptor is an inhibitory regulative G-protein coupled receptor ($G_i$), which downregulates the intracellular second messenger cyclic adenosine monophosphate. Functionally, the presence of the α-2 receptor on the presynaptic membrane forms part of a negative-feedback mechanism regulating the presynaptic release of noradrenaline. Therefore, as the synaptic concentration of noradrenaline increases, the subsequent increase in presynaptic α-2 receptor activation further downregulates neurotransmitter release.[1,2]

Because of its imidazole ring-based structure, clonidine demonstrates activity at imidazoline receptors. To date, 3 classes of imidazoline receptors have been identified ($I_1$–$I_3$). The $I_1$ receptor is found centrally, where it is thought to inhibit catecholamine synthesis and suppress the activity of the sodium-hydrogen antiporter.[3] Animal studies suggest that the $I_1$ receptor is likely to be involved in the hypotensive response seen with clonidine.[3,4] Meanwhile $I_2$ receptors may have a role in the modulation of chronic pain and monoamine synthesis,[5] whilst $I_3$ receptors appear to modulate the secretion of insulin from pancreatic β-cells.[6]

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## Pharmacokinetics

It is presented for intravenous (IV) formulation as the hydrochloride salt of clonidine to allow water solubility in solution, in a vial of 150 μg for reconstitution. When administered in vivo, it is highly lipid soluble, which allows it to cross the blood-brain barrier effectively. It is well absorbed orally, with a bioavailability of 70% to 80%. When given IV, the plasma concentration follows a biexponential decay model, with a distribution half-life of 20 minutes as the drug enters tissues with high blood flow and a terminal elimination half-life of 12 to 16 hours. It is only 20% protein bound, with an average volume of distribution of about 2l/kg. Clonidine is about 50% metabolised in the liver by the cytochrome P-450 system; the remaining 50% is excreted unchanged in the urine.

## Pharmacodynamics

### Central Nervous System

Whilst clonidine has both centrally and peripherally mediated analgesic properties, its efficacy in postoperative pain management remains contested. It is often described as part of a multimodal approach to analgesia, particularly in combination with opioids, where it is reported to augment the analgesic effect of opioids without reducing respiratory depression.[1,7] Centrally, it is thought to act on α-2 receptors in the substantia gelatinosa of the dorsal horn, where it has the effect of increasing acetylcholine and suppressing the release of substance P and glutamate. Peripherally, clonidine appears to block C-fibres and interact with inhibitory G-proteins.[8]

### Cardiovascular

Clonidine administration produces a well-recognised centrally mediated hypotension and reduction in heart rate, as a result of sympatholisis because of its effects on the presynaptic α-2 receptor and also the $I_1$ receptor, as outlined above. There is also the potential for a peripherally mediated hypertensive effect, which is usually associated with higher IV doses of clonidine. This is thought to be due to the activation of peripheral postsynaptic α-2b receptors (a subclass of α-2 receptor found on vascular smooth muscle), coupled with the increasing activation of α-1 receptors at higher doses, due to the nonspecific nature of clonidine at alpha receptors. The combination of agonism at both α-1 and peripheral α-2b receptors may produce a vasoconstrictive effect and increase in systemic vascular resistance, which is paradoxical to the anticipated sympatholytic effects associated with agonism of the presynaptic α-2 receptor.[9] This initial hypertensive response is transient and not always observed in routine clinical use. Sudden withdrawal of clonidine therapy can lead to rebound hypertension and tachycardia, and so care must be taken to titrate clonidine infusions down rather than stopping therapy abruptly.

### Respiratory

Clonidine administration does not produce any clinically significant respiratory depression, unless given in very large doses, nor does it potentiate opioid-induced respiratory depression.[1]

### Gastrointestinal and Endocrine

Clonidine has the advantage of decreasing gastrointestinal secretions when used as a premedication but does not appear to affect gastric pH significantly.[1] One of the primary uses for clonidine is to obtund the sympathoadrenal stress response to surgery, and as would be anticipated, clonidine reduces catecholamine secretion from the adrenal medulla.[10] Unlike other imidazole ring–containing drugs such as etomidate, clonidine does not appear to affect steroidogenesis. There is also some evidence that clonidine may suppress insulin release from pancreatic β-cells through its action on the $I_3$ receptor, although the clinical effects of this are likely to be negligible.[6] Clonidine has also been shown to produce a mild diuresis through the inhibition of antidiuretic hormone release.[11]

# CLINICAL USES IN ANAESTHESIA AND CURRENT EVIDENCE

It is vital to note that the following clinical uses of clonidine are not mainstream. This article explores the uses of clonidine in the intensive care unit (ICU) and anaesthesia with evidence supporting its use. Therefore, it is important for clinicians to make the appropriate and careful decision in administering clonidine, taking into consideration the clinical indication, dosing, and route of administration.

## Sedation

The goals of ICU sedation are to provide analgesia and anxiolysis and to achieve a sedative state in which a patient cooperates with interventions and health care providers.[12]

Alpha-2 adrenoceptor agonists are useful in the high-dependency unit and ICU as they are capable of producing dose-dependent sedation with minimal impairment of respiratory function, unlike other sedative drugs.[13] Other characteristics of α-2 adrenoceptor

agonists that make them extremely desirable in critical care settings include sedation that is easily reversed without pharmacologic agents, analgesic and anxiolytic properties, reduced oxygen consumption, and preserved renal function.[14]

A recent placebo-controlled, randomised study reported use of 4 μg $kg^{-1}$ $h^{-1}$ IV infusion of clonidine (maintaining a plasma concentration of approximately 1.7 ng $ml^{-1}$) for a duration of 1 hour that resulted in good analgesia to a cold pressor test and satisfactory sedation that was overcome by verbal simulation in a normal or loud voice.[15] This was supported by several other studies that have suggested a dose range of 4 μg $kg^{-1}$ $h^{-1}$ for adequate sedation.[14] Although mean arterial pressure and heart rate were noted to decrease during clonidine infusions, the studies did not report significant haemodynamic instability at these doses.

It is important to note that dexmedetomidine (α-2 adrenoceptor agonist) is more commonly used than clonidine in the United States and some European countries for intensive care sedation and has also been licensed for sedation of nonintubated patients before or during the operation.[16] Dexmedetomidine is 8 times more specific for α-2 adrenoceptors than clonidine, and because of its improved specificity for the α-2 adrenoceptors, it can be considered a more effective sedative than clonidine.[17]

A prospective study in England[18] showed that clonidine can be used as an effective alternative sedative to opioids in children, with a recommended paediatric dose range of 0.2 to 2.0 μg $kg^{-1}$ $h^{-1}$. This, combined with a low-dose infusion of midazolam (50 μg $kg^{-1}$ $h^{-1}$), provided dose-dependent sedation in ventilated critically ill children.[18]

## Analgesia

Clonidine acts as a useful adjunct in postoperative analgesia and reduces narcotic requirements in a dose-dependent manner. However, there has been no consensus on the optimal dose or method of administration.

A double-blind randomised controlled trial (RCT) showed that an initial loading dose of IV clonidine 5 μg $kg^{-1}$ given in the first hour postoperation and a maintenance dose of IV infusion of 0.3 μg $kg^{-1}$ $h^{-1}$ provided long-lasting stable analgesia and reduced morphine requirements.[19] The study also showed that administering a loading dose of 5 μg $kg^{-1}$ of clonidine immediately postoperatively helps achieve early control of tachycardia during emergence from anaesthesia with no bradycardia or hypotension. Although a loading dose of 5 μg $kg^{-1}$ helped achieve better analgesia, the degree of hypotension and sedation was more severe.

A recent double-blind RCT[20] demonstrated the optimal dose to be a 3 μg $kg^{-1}$ bolus dose followed by a continuous infusion of 0.3 μg $kg^{-1}$ $h^{-1}$. It is important to note the dose-dependent side effects of administering IV clonidine, including hypotension, bradycardia, and cardiac arrest.[21] The POISE-2 study looked at the effects of administering clonidine in surgical patients at risk of cardiovascular events and found that nonfatal cardiac arrest was increased when clonidine was administered in these patients. Hence, extra caution must be taken when administering IV clonidine in patients with known risk factors for cardiovascular events. Alternatively, intramuscular clonidine 2 μg $kg^{-1}$ can be administered as an adjunct to opioids for adequate analgesia for minor orthopaedic operations.[22]

Oral clonidine (5 μg $kg^{-1}$) administered 1.5 hours before surgery and at 12 hours and 24 hours after initial dose can be used as an effective adjunct for postoperative analgesia and can help decrease patient-controlled analgesia morphine requirements by 37%.[23]

It is important to note the existence of a black box warning of administering epidural clonidine for obstetrical, postpartum, and perioperative pain management because of its adverse risk of haemodynamic instability.

Using clinical indication and taking into account the contraindications for the different routes of administration, the clinician can choose the appropriate route of administration for achieving better postoperative analgesia for patients.

## General Anaesthesia

A recent RCT showed that a preanaesthetic oral clonidine dose of 150 μg reduces the total requirement of propofol by 41%[24] in breast cancer patients undergoing minor breast-conservative surgery. The dose of 150 μg of oral clonidine was also shown to attenuate the sympathetic haemodynamic responses associated with tracheal intubation.[24]

In children, an oral clonidine dose of 4 μg $kg^{-1}$ has been shown to successfully decrease the minimum alveolar concentration of sevoflurane by 40%.[25]

Intravenous clonidine has been shown to cause a significant decrease in the bispectral index during total IV anaesthesia and allows lower general anaesthetic requirements to provide a similar level of anaesthesia without intraoperative awareness or prolonged recovery times.[26]

## Motor and Sensory Block

Clonidine has been used as an adjunct to local anaesthetics in various regional techniques to prolong the duration of blocks.[27] A recent systematic review showed that the duration of motor and sensory block was prolonged by 47 minutes on average

when clonidine was added to intrathecal local anaesthetics.[28] However, the study did not disclose an optimal dose and included a dose range from 15 μg to 150 μg.

A dose of 3 μg $kg^{-1}$ of IV clonidine administered immediately after the spinal block showed prolongation of the block by approximately 60 minutes without any notable adverse side effects.[29]

In addition, it must be noted that although we know the mechanism of action of clonidine in the neuraxial technique, there is no established mechanism of action of clonidine in peripheral nerve block. A double-blind RCT looked at the effects of clonidine in prolonging the duration of axillary nerve block and showed that there was no difference in duration of the block with or without clonidine.[30]

## OTHER CLINICAL USES OF CLONIDINE

Opioid-induced hyperalgesia is a known phenomenon that occurs when prolonged opioid administration results in an abnormal and increased sensitivity to painful stimuli.[31] Opioid-induced hyperalgesia is thought to occur as a result of the activation of the N-methyl-d-aspartate receptor by μ-receptor agonists, such as remifentanil. Intravenous clonidine is known to reduce the intensity of opioid-induced analgesia.[32]

Clonidine can be an effective adjunct in managing the symptoms of alcohol withdrawal. α-2 agonists such as clonidine decrease noradrenaline release and reduce alcohol withdrawal symptoms by reducing the sympathetic overdrive. This helps with managing symptoms of withdrawal, including anxiety, agitation, and tremor.[33]

Postanaesthetic shivering occurs in up to 65% of patients and can cause significant distress to patients because of the increase in global oxygen demand. Intravenous clonidine 150 μg given at induction of anaesthesia can help reduce or prevent postanaesthetic shivering.[34]

Clonidine can be used as an effective adjunct in the prevention of the emergence of delirium and agitation for children who have received sevoflurane or isoflurane for general anaesthesia. A dose of 2 to 3 μg $kg^{-1}$ of IV clonidine can be administered following induction of anaesthesia to help prevent and improve emergence agitation postoperatively.[35,36]


## SUMMARY

Clonidine is an imidazole compound that was developed for its antihypertensive properties. However, there is growing evidence for its place in anaesthetics and perioperative medicine. It possesses interesting pharmacological properties that can make it an appropriate and effective adjunct in anaesthetic practice, including sedation, reduction in general anaesthetic and postoperative opioid requirements, and prolongation of sensory blockade. Clonidine can be administered through different routes including oral, IV, and intrathecal, which allows it to be used in a multitude of situations. Despite the existence of studies supporting clinical uses of clonidine in anaesthesia, there are not enough data from large RCTs and therefore not enough evidence to support the routine use of clonidine in anaesthetic practice. Although it is a versatile drug, there has been no consensus on the dosing, and careful titration to effect is required to minimise its intra- and postoperative side effect profile.


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