

NEWER DRUGS IN ANAESTHESIA**TEENA BANSAL*, SARLA HOODA****

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Anesthesiology is on the verge of a major evolution that will involve newer, more specific and better anaesthetic agents and newer, safer and simpler techniques to deliver these agents. Why we need new drugs is the first question. We need them because the drugs we have today can cause damage and even death if given incorrectly. We need better and safer anaesthetics¹. New drugs in anaesthesia are classified as given below

1. Premedication

- Dexmedetomidine
- Clonidine

2. Induction

- Xenon

3. Muscle relaxation

- Cisatracurium

4. Analgesia

- Remifentanyl

1. Dexmedetomidine

Dexmedetomidine is the most recent alpha-2 agonist approved by FDA in 1999 for use in humans for analgesia and sedation². The mechanism of action of dexmedetomidine differs from clonidine as it possesses selective alpha-2 adrenoceptor agonism especially for the 2A subtype of this receptor, which causes it to be a much more effective sedative and analgesic agent than clonidine. The sedative properties are facilitated through the locus coeruleus site in the CNS and analgesic effects may occur via activation of the alpha2 receptors by augmenting the action of opioids.

Pharmacodynamics- Dexmedetomidine has no direct effect on heart. It has a biphasic effect on the cardiovascular system. Initial bolus injection is associated with vasoconstrictive effects causing bradycardia and hypertension whereas continuous infusion is associated with hypotension secondary to vasodilatation caused by central sympatholysis³. Bradycardia and hypotension are amenable for treatment by atropine, ephedrine or volume infusions. However, these effects may be deleterious in hypovolemic patients or patients with fixed stroke volume⁴. The respiratory depression caused by dexmedetomidine has been reported to be much less than with other sedatives.

Pharmacokinetics- Dexmedetomidine undergoes almost complete hydroxylation through direct glucuronidation and cytochrome P₄₅₀ metabolism in liver. Metabolites are excreted in the urine (about 95%) and in the feces (4%). It is unknown whether they possess intrinsic activity. The elimination half life is approximately 2 hours². It may be necessary to decrease the dose in patients with hepatic failure, since they have lower rates of metabolism of the active drug. In cases of renal failure, the metabolites may accumulate, the effects of which have not yet been studied. The average protein binding of dexmedetomidine is 94% with negligible protein binding displacement by fentanyl, ketorolac, theophylline, digoxin and lidocaine, drugs commonly used during anaesthesia and in the ICU².

Side effects- The teratogenic effects of dexmedetomidine are not studied yet but this drug shows placenta transfer; therefore it should be used during pregnancy only if it gives a definite advantage over other drugs. The common side effects are hypotension (30%) and bradycardia (10%).

Dosage and route of administration- It is given intravenously. Loading is done at 1 µg/kg for 10 minutes; then given by continuous infusion at rate of 0.2-0.7 µg/kg/h. The advantages are anxiolysis, analgesia, easy arousal and no respiratory depression.

Uses during anaesthesia and critical care- Dexmedetomidine possesses anxiolytic, sedative, analgesic and sympatholytic properties. It may be used as premedicant, adjunct to balanced anaesthesia as it remarkably reduces the doses of the anaesthetic drugs. It also reduces the sympathoadrenal responses during laryngoscopy and intubation. It can also be used as sole analgesic drug in healthy and young patients for minor procedures⁵. Postoperative analgesia and sedation with arousability and minimal respiratory depression remains the main use of dexmedetomidine. All effects of dexmedetomidine could be easily antagonized by administering the alpha-2 adrenoceptor antagonist atipamezole, which, like dexmedetomidine, reverses sedation and sympatholysis and has a half life of 1.5-2 hours. The combination of dexmedetomidine and atipamezole might be the basis for a reversible intravenous anaesthetic technique that could provide timely independent recovery from anaesthesia and sedation in the future⁶.

2. Clonidine

Clonidine was introduced into clinical practice in 1966 as a centrally acting antihypertensive agent. Clonidine is an imidazoline derivative with alpha 2 adrenergic agonistic activity with an α₂:α₁ ratio of 200:11. The drug is licensed for the treatment of hypertension, migraine and menopausal flushing⁷. It is also an analgesic, sedative and anxiolytic. These properties along with its ability to maintain perioperative hemodynamic stability make clonidine a useful agent in anaesthesia and intensive care.

Mechanism of action- Clonidine acts by stimulating the presynaptic alpha 2 adrenoceptors, thereby decreasing noradrenaline release from both central and peripheral sympathetic nerve terminals. The effects of clonidine occur due to its action both at spinal and supraspinal sites, including depression of thalamic transmission of impulses to the cerebral cortex as well as enhancement of descending inhibitory pathways to the dorsal horn⁸. Alpha 2 adrenoceptors are found postjunctionally on the dorsal horn neurons of the spinal cord and acts by inhibiting the release of substance P. Clonidine also acts on the cholinergic, purinergic and serotonergic pain systems causing analgesia⁹. **Pharmacokinetics-** Clonidine is rapidly and well absorbed orally with a bioavailability of 100%. It is very lipid soluble and penetrates the central nervous system. It is 20% protein bound in the plasma. It is metabolized in liver to inactive metabolites and 65% of the dose is excreted unchanged in urine, 20% is excreted in feces. The elimination half life is 6-23 hours (average 7.7 hours) which is markedly increased in renal impairment requiring a dose reduction¹⁰. The peak action occurs in 10 minutes and lasts for 3-7 hours after single intravenous

dose. On oral administration, it reaches a peak plasma level within 60-90 minutes⁹.

Pharmacodynamics-

- i) **Central nervous system:** Clonidine produces dose related sedation, analgesia, anxiolysis and a reduction in the requirements of other anaesthetic agents and opioids⁹.
- ii) **Cardiorespiratory system:** Clonidine causes an initial short lived increase in blood pressure and systemic vascular resistance and a decrease in cardiac output due to activation of postjunctional alpha 2 receptors on the peripheral vasculature. This is accompanied by a long lasting decrease in heart rate and blood pressure resulting from a centrally mediated decrease in sympathetic tone and an increase in vagal activity. Clonidine causes very minimal respiratory depression along with good sedation. There is no change in respiratory rate, PaCO₂, SpO₂ on administration¹¹.

Side effects- Dryness of mouth (50%), sedation, respiratory depression, fluid retention and constipation have been reported. Rapid withdrawal of drug leads to life threatening rebound hypertension and tachycardia⁸.

Clinical applications- It is presented as a clear colourless solution for injection containing 150 micrograms in 1 ml ampoule. It is administered by I.V, intrathecal, extradural, intramuscular, transdermal and intraarticular routes¹².

Current recommendations of use of clonidine in the perioperative period-

- Premedication
- As Anxiolytic
- For Sedation
- To prevent or treat shivering
- Treatment of hypertensive crisis
- To prolong the duration of epidural or spinal anaesthesia
- Treatment of intraoperative and postoperative pain
- Treatment of intraarticular pain
- To obtund the pressor response during endotracheal intubation
- Treatment of cancer pain

Dosage guidelines-

- a) **Intrathecal:** A 15-30 µg of clonidine added to local anaesthetic agent provides most of the benefits without any significant side effect. The maximum dose is 1 µg/kg. Clonidine prolongs the sensory blockade and reduces the amount of local anaesthetic required to produce analgesia.
- b) **Epidural:** A 50 µg or 1 µg/kg (whichever is lower) dose of clonidine added to local anaesthetic agent provides most of the benefits without any significant side effect. The maximum dose is 2µg/kg¹³.
- c) **Intraarticular:** A 150 µg or 2 µg/kg (whichever is lower) dose of clonidine added to local anaesthetic agent provides better and longer effects without any significant side effect.
- d) **Perineural:** 1 µg/kg added to local anaesthetic agent prolongs the duration of analgesia.
- e) **Intravenous:**
- i) A dose of 50 to 75 µg clonidine or 1µg/kg (whichever is lower) administered slowly over 15 minutes prior to surgery provides most of the benefits without any significant side effect.

ii) For treatment of hypertensive crisis 150 to 300 µg is given by slow i.v. injection over 10 minutes. The maximum dose is 3 µg/kg.

iii) For postoperative shivering the dose is 30 µg i.v. slowly.

Use during pregnancy and lactation- It is not indicated during pregnancy and lactation as it crosses the placental barrier and is secreted in breast milk also.

Overdosage and treatment- There is no specific antidote. Most cases require general supportive measures.

3. Xenon

Xenon has been used as a general anaesthetic. Although it is expensive, anaesthesia machines that can deliver xenon are available in European market, because advances in recovery and recycling of xenon have made it economically viable¹⁴.

Two physiological mechanisms for xenon anaesthesia have been proposed. The first one involves the inhibition of the calcium ATPase pump-the mechanism cells use to remove calcium -in the cell membrane of synapses¹⁵. The second mechanism focuses on the non specific interactions between the anaesthetic and the lipid membrane.

Xenon has a minimum alveolar concentration (MAC) of 72 % at age 40, making it 44% more potent than N₂O as an anaesthetic¹⁶. Thus it can be used in concentrations with oxygen that have a lower risk of hypoxia. Unlike N₂O, xenon is not a greenhouse gas and so it is also viewed as environmentally friendly¹⁷. Xenon vented into the atmosphere is being returned to its original source, so no environmental impact is likely.

4. Cisatracurium besilate

Physical structure- Cisatracurium is a bis benzyl tetrahydro isoquinolinium agent with an intermediate duration of action. It is a stereoisomer of atracurium that is 4 times more potent. Atracurium contains approximately 15% cisatracurium.

Metabolism and excretion- Cisatracurium is metabolized by Hofmann elimination. But unlike atracurium, it does not cause release of histamine in the clinical dose range¹⁸. The resulting metabolites (a monoquaternary acrylate and laudanosine) have no intrinsic neuromuscular blocking effects¹⁹. Because of its higher potency, the amount of laudanosine produced is significantly less than atracurium. Metabolism and elimination appear to be independent of renal or liver failure. Minor variations in pharmacokinetic patterns due to age do not tend to result in clinically significant changes in duration of action.

Dosage- Cisatracurium produces good intubating conditions following a dose of 0.1-0.15 mg kg⁻¹ within 2 minutes. The average infusion rate ranges from 1.0-2.0 µg/kg/min. Thus it is equipotent with vecuronium and more potent than atracurium²⁰.

Cisatracurium should be stored under refrigeration (2-8°C) and should be used within 21 days after removal from refrigeration and exposure to room temperature.

Side effects and clinical considerations- Unlike atracurium cisatracurium does not cause release of histamine in the clinical dose range¹⁸. It does not affect heart rate or blood pressure, nor does it produce autonomic effects, even at doses as high as eight times ED₉₅.

5. Remifentanyl

Remifentanyl is a selective mu opioid agonist with an analgesic potency similar to that of fentanyl (15-20 times as potent as alfentanil) and a blood-brain equilibration time similar to that of alfentanil²¹. It is structurally unique because of its ester linkage. Remifentanyl's ester structure renders it susceptible to hydrolysis by nonspecific plasma and tissue esterases to inactive metabolites²². This unique pathway of metabolism imparts to remifentanyl (a)

precise and rapidly titrable effect due to its rapid onset and offset (b) noncumulative effects and (c) rapid recovery after discontinuation of its administration.

Pharmacokinetics- Pharmacokinetics of remifentanyl is characterized by small volume of distribution, rapid clearance and low interindividual variability compared to other I.V. anaesthetic drugs. The rapid metabolism of remifentanyl and its small volume of distribution mean that remifentanyl will accumulate less than other opioids. Because of its rapid systemic clearance, remifentanyl provides pharmacokinetic advantages in clinical situations requiring predictable termination of drug effect²². It's pharmacokinetics are similar in obese and lean patients confirming that clinical dosing regimens should be based on ideal (lean) body mass rather than total body weight²³.

Metabolism- Remifentanyl is unique in undergoing metabolism by nonspecific plasma and tissue esterases to inactive metabolites²². The principal metabolite, remifentanyl acid is 300 to 4600 fold less potent than remifentanyl and is excreted primarily by the kidneys. Remifentanyl's pharmacokinetics is unchanged by renal or hepatic failure because esterase metabolism is usually preserved in these states²⁴. It's elimination half time is 6 minutes and context sensitive half time is about 4 minutes.

Clinical uses- The clinical uses of remifentanyl reflect the unique pharmacokinetic profile of this opioid, which allows rapid onset of drug effect, precise titration to the desired effect, the ability to maintain a sufficient plasma opioid concentration to suppress the stress response and rapid recovery from the drug's effects. In cases where a profound analgesic effect is desired transiently (performance of a retrobulbar block), remifentanyl may be useful. Prompt onset and short duration of action make remifentanyl a useful selection for suppression of the transient sympathetic nervous system response to direct laryngoscopy and tracheal intubation in at risk patients²⁵. Intermittent remifentanyl administered as patient controlled analgesia is an effective and reliable analgesic during labour and delivery²⁶. Remifentanyl can be used for long operations, when a quick recovery time is desired (neurologic assessment, wake up test). Anaesthesia can be induced with remifentanyl 1 µg/kg i.v. administered over 60-90 seconds. Dose for analgesia is 0.25 to 1.00 µg/kg i.v.

Side effects- The advantage of remifentanyl possessing a short recovery period may be considered a disadvantage if the infusion is stopped suddenly. It is important to administer a longer acting opioid for postoperative analgesia when remifentanyl has been administered for this purpose intraoperatively. It has been reported to induce seizure like activity²⁷. Nausea and vomiting, depression of ventilation and mild decreases in systemic blood pressure and heart rate may accompany the administration of remifentanyl. Placental passage of remifentanyl is prompt but neonatal effects do not seem to occur.

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