

PHARMACOLOGY OF CISATRACURIUM BESYLATE

Abstract :

Background: In routine anesthesia practice, a variety of neuromuscular blocking agents are used. Cisatracurium besylate is a nondepolarizing neuromuscular blocking agent with an intermediate duration of action. Because of the high molecular weight and polarity, the volume of distribution is small. Cisatracurium besylate undergoes Hofmann elimination, making it an excellent choice for patients suffering from organ failure.

Methodology: This review article was prepared after a thorough study of the literature using data search engines such as Scopus, Pubmed, Web of Science, and Google Scholar. This article referred to prior Cisatracurium observational studies and case reports.

Review findings: After learning pharmacology, uses, contraindications of Cisatracurium and reviewing the previous observational studies and case reports about Cisatracurium, this drug is used as a muscle relaxant during general anesthesia for tracheal intubation. It has been used successfully in critical care settings where patients were placed on mechanical ventilation and required complete skeletal muscle paralysis. Systemic or cutaneous release of histamine is not caused by cisatracurium.

Conclusion: Cisatracurium is a relatively new intermediate-onset, long-lasting skeletal muscle relaxant. This medication can be used safely in patients with hepatorenal impairment. It, like other muscle relaxants, can be used during elective surgical repair under general anaesthesia as well as in patients undergoing prolonged controlled mechanical ventilation. The only concern could be the cost effectiveness in comparison to other skeletal muscle relaxants on the market.

Keywords: Cisatracurium, Neuromuscular blocking agent, Nondepolarizing

Introduction:

General anaesthesia produced by different anaesthetic agents can be described as having amnesia, a controlled reversible state of unconsciousness with absence of pain sensation over the whole body, and muscular relaxation of a greater or lesser degree. In the actuation of general anaesthesia, a swift, precise, and prudent practice of endotracheal intubation is vital. In 1942, when Griffith and Johnson introduced d- tubocurarine, a neuromuscular blocking agent, into clinical practice, a new era commenced in anaesthesia and surgery. (1)NMBD is seen as an adjuvant to general anaesthesia to assist with endotracheal intubation and to unwind skeletal muscles during surgery. It can also be used in an intensive care unit to provide skeletal muscle relaxation to aid mechanical ventilation, but it must be used in conjunction with sedation.

Objectives:

Chemistry

Pharmacology

Indications of cisatracurium.

The side effects of cisatracurium.

Reversal medications for cisatracurium.

Special population group

Chemistry:

Cisatracurium is an intermediate-acting bis-benzylisoquinolinium skeletal muscle relaxant. It is one of the 10 isomer of the atracurium which has the similar profile(1). The molecular formula of the Cisatracurium parent bis-cation is C₅₃H₇₂N₂O₁₂, and its molecular weight is 929.2. Cisatracurium has the molecular formula C₆₅H₈₂N₂O₁₈S₂ and the molecular weight 1243.50 as a besylate salt(2).

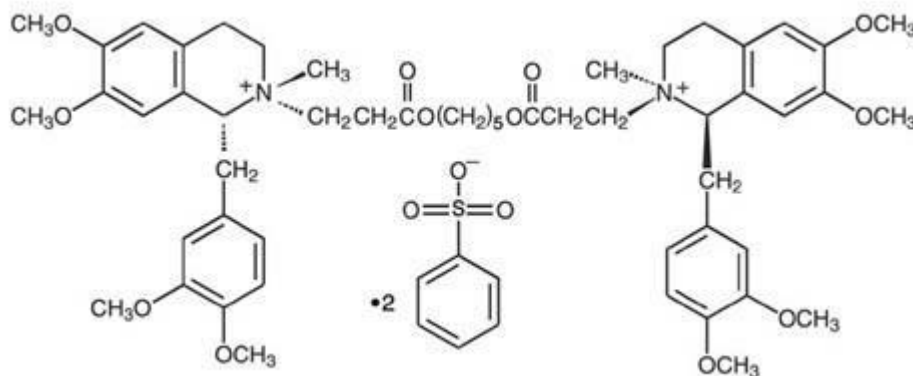


Figure 1: Chemical structure of Cisatracurium

STABILITY:

Cisatracurium is a benzenesulfonic acid-adjusted aqueous solution with a pH range of 3.25 to 3.65.

To maintain potency, cisatracurium should be stored in a carton at temperatures ranging from 2 to 8° C. Cisatracurium besylate gives up effectiveness at a rate of about 5% per year when stored in the fridge (5°C).

It is stable at 4° C for 30 days in a D 5% and 0.9 % Normal saline solution(3) (4).

Pharmacology:

Mechanism of action:

It works by vying for nicotinic cholinergic receptors at the motor endplate with the neurotransmitter acetylcholine without causing depolarization. The fade phenomenon on repetitive nerve stimulation is observed with cisatracurium, as with other NMBD agents, indicating activity at presynaptic nicotinic receptors. (2)

The following diseases can cause hypersensitivity to NMBDs:

Amyotrophic lateral sclerosis (ALS)

Autoimmune conditions

Lupus erythematosus (SLE)

Polymyositis

Dermatomyositis

Periodic paralysis in a family hyperkalemia

Guillain-Barré syndrome

Dystrophy of the muscles (Duchenne type)

Myasthenia gravis

Myasthenic syndrome

Myotonia Dystrophic

Diseases that can lead to NMBD resistance are listed below:

Injury from a fire

Cerebral palsy

Hemiplegia (on the affected side)

Denervation of the muscles (peripheral nerve injury)

Chronic severe infection

Tetanus

Botulism



Figure 2: Vial of Cisatracurium

POTENCY:

- With an ED95 of 0.05 mg/kg, cisatracurium is approximately three times as potent as atracurium during balanced anesthesia.
- To assess the potency of neuromuscular blockers, The equivalent dose of the neuromuscular blocking drug is required to create an effect (e.g., 50%, 90%, or 95% twitch range depression; usually described as ED50, ED90, and ED95, respectively) is used.
- Effective dose for 50% depression of twitch height (ED50) 0.026mg/kg (0.015 to 0.031).
- Effective dose for 95 % depression of twitch height (ED95) 0.05mg/kg (0.048 to 0.053)(5) (6).

Dosage:

The dose used to facilitate tracheal intubation has traditionally been twice the ED95, i.e., 0.1mg/kg cisatracurium. Cisatracurium dosage varying between 2 ED95 to 8 ED95 can be used.

The maintenance dose is about a fourth of the initial dose.

PHARMACODYNAMICS:

Cisatracurium is a new skeletal muscle relaxant that primarily acts on cholinergic receptors, blocking impulses transmitted to skeletal muscle. Compared to other skeletal muscle relaxant drugs, the onset and duration of action are intermediate. Acetyl cholinesterase inhibitors such as neostigmine primarily reverse the action, thereby antagonizing the action of cisatracurium.

Cisatracurium has approximately three times the neuromuscular blocking potency of atracurium besylate. Cisatracurium efficiently achieve doses that take up to 2 minutes longer to reach maximum block than atracurium besylate. At effective doses, cisatracurium and atracurium besylate has potent durations of action and rates of spontaneous recovery that are comparable.

The pharmacodynamics of cisatracurium doses ranging from 2 to 8 ED95 given over 5 to 10 seconds during balanced anesthesia. The pharmacologic duration of block increases by approximately 25 minutes when the dosages are doubled. Once recovery begins, the rate of restoration is dose insensitive(4) (7).

Hemodynamic Profile:

Cisatracurium, unlike atracurium, can be given as a fast bolus at increased multiples of the ED95 due to its cardiovascular profile. Cisatracurium has no dose-related impacts on mean arterial blood pressure (MAP) or heart rate (HR) in regular adult patients or patients with severe heart disease after doses ranging from 2 to 8 ED95 (> 0.1 to > 0.4 mg/kg) given over 5 to 10 seconds (7) (8).

PHARMACOKINETICS:

Cisatracurium's neuromuscular blocking interaction is contributed to the active substance. Cisatracurium plasma concentration-time metrics after an IV carbo load are better defined by a two-compartment open prototype (with elimination from both compartments) with a half-life ($t_{1/2}$) of 22 minutes, a plasma clearance (CL) of 4.57 mL/min/kg, and a volume of distribution (V_{ss}) of 145 mL/kg (7) (6) (4).

METABOLISM:

The breakdown of cisatracurium is entirely independent of liver metabolism. Hofmann elimination (a pH and temperature-dependent chemical process) virtually eliminates cisatracurium to form the monoquaternary acrylate metabolite and laudanosine, none of which have neuromuscular blocking activity (5) (9). Laudanosine may be further degraded to form desmethyl metabolites, which are conjugated with glucuronic acid and excreted in the urine(10).

Elimination, Clearance, and Half-life :

Cisatracurium CL values in better and healthier surgical patients ranged from 4.5 to 5.7 mL/min/kg. According to fractional pharmacokinetic prediction, Hofmann elimination accounts for roughly 80% of CL, with renal and hepatic eradication accounting for the remaining 20%. These results supported the low interpatient variability in CL (16%) estimated in population PK/PD evaluates and parent and metabolite recovery in urine(3).

INDICATIONS AND USAGE:

1. cisatracurium is a neuromuscular blocking agent with an intermediate onset/intermediate duration that is an adjunct to general anesthesia to facilitate tracheal intubation.
2. To relieve skeletal muscle tension during surgery.
3. ICU patient on mechanical ventilation.

Contraindication:

In patients who have a history of hypersensitivity to the product or its components and those who have malignant hyperthermia or neuromuscular disorders.

ADVERSE REACTIONS :

Incidence > 1%: None

Incidence < 1% occurrence :

Bradycardia of the heart (0.4 percent)

hypertension (0.2 percent) scrubbing (0.2 percent)

Bronchospasm of the lungs (0.2 percent)

Rashes on the skin (0.1 percent)

Autonomic effects: Autonomic margin of safety of the relaxant is the dose-response ratio, comparing the neuromuscular blocking potency with their potencies for blocking vagal or sympathetic blockade. Cisatracurium has little or no tendency to cause hypotension, tachycardia, bradycardia, or dysrhythmia.

Histamine release: Systemic or cutaneous release of histamine is not caused by cisatracurium(6) (7).

Antagonism of Neuromuscular Block :

0.04 to 0.07 mg/kg neostigmine was given in an estimate of 9 to 10 minutes after roughly 10% recovery from neuromuscular block (range: 0 percent to 15 percent). This contributed to a 95% revival of muscle twitch reaction and a 70% revival of the T4:T1 ratio. Following these neostigmine injections, the minimum duration from 25% recovery of muscle twitch

response to 70% T4:T1 ratio was 7 minutes. Following the reversal, the overall average index ranged from 25% to 75% and took 3 to 4 minutes(7) (8).

Toxicity:

An large dose of cisatracurium may end up causing neuromuscular blockade that can last the longest amount of time required for surgery and anesthesia. The patient is sedated, with a patent airway, and on governed ventilation until the neuromuscular function is regained. It should be noted that if complete neuromuscular blockade is present or suspected, the reversal should never be attempted. The neuromuscular blockade can be altered using an anticholinesterase agent (e.g., neostigmine) in a mixture with an anticholinergic agent after recovery from blockade is demonstrated by peripheral nerve stimulation (7)

Drug interactions:

Interaction among nondepolarizing neuromuscular blockers: Combining structurally different drugs like rocuronium - mivacurium or rocuronium – cisatracurium produces a synergistic response.

Inhaled anesthetics: Inhalation agents potentiate the neuromuscular blocking effect of cisatracurium by various mechanisms.

Other drugs that may enhance nondepolarizing agents' neuromuscular blocking action include:

Certain antibiotics (such as aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistemetate), magnesium salts, lithium, local anesthetics, procainamide, and quinidine are examples.

Nondepolarizing neuromuscular blocking agents' resistance to neuromuscular blocking action: In patients who have been taking phenytoin or carbamazepine for a long time.

CISATRACURIUM BESYLATE IN DIFFERENT PATIENT GROUPS

The Paediatrics age group:

For children below two years, cisatracurium is a safe and effective neuromuscular drug due to its fast onset and short duration of action. Muscle relaxation may be prolonged in neonates and infants as the volume of distribution is more excellent. Lack of histamine release and low incidence of adverse effects have made cisatracurium a worthwhile neuromuscular blocking drug than older NMBA's like pancuronium and vecuronium. Recovery time is also shorter than in adults (11).

The Geriatrics age group:

Since plasma clearance reduces with age, the volume distribution of cisatracurium also decreases in geriatric patients. As a result duration of action gets prolonged. A single bolus dose does not have much effect on the recovery profile. The elderly had a higher distribution volume, which contributed to a slight increase in elimination half-life(7) (5) (11).

The Obstetrics:

As a result of the physiological changes in pregnancy, body weight, plasma volume, and blood volume increase, but cisatracurium remains unaffected in volume distribution in pregnancy. The highest concentration which gets into the neonate was less than one-third of the amount of drug needed to bring about a 50% neuromuscular block in infants.

Variation with gender:

Cisatracurium has slightly greater potency in women than in men.

ED₉₅ of cisatracurium in male patients 67.4±4.4 µg/kg.

ED₉₅ of cisatracurium in female patients 48.7±1.0 µg/kg.

Variation in the onset time ($p < 0.05$) was insignificant.

Patients with hepatic dysfunction:

Cisatracurium undergoes spontaneous degradation, which makes it an ideal neuromuscular blocking agent for patients complicated with liver or renal disease. Hence dose modification is not needed in liver failure (4) (12) (11).

Patients with renal Failure:

Roughly 77% of cisatracurium is removed by Hoffmann elimination, and 16% by renal excretion. Cisatracurium has no significant adverse effects because its duration of action is not prolonged in patients with kidney dysfunction(2).

Intensive Care Unit (ICU) Patients:

Cisatracurium and atracurium have comparable plasma clearances. Cisatracurium had a greater distribution volume and a lengthier t_{1/2} than atracurium. The interactions among plasma cisatracurium or atracurium concentration levels and neuromuscular block in ICU patients have not been researched(4).

METHODOLOGY:

This review article was prepared after a thorough study of the literature using data search engines such as Scopus, Pubmed, Web of Science, and Google Scholar. This article referred to cisatracurium besylate prior observational studies and case reports

DISCUSSION:

Kisor DF and Schmith VD published Clinical Pharmacokinetics of Cisatracurium Besilate in 1999. A 2-compartment prototype best represents the concentration versus time characteristic of cisatracurium besylate after a 5- to 10-second i.v bolus dose in good health young adult post-operative, elderly, and patients with renal or hepatic failure. Cisatracurium besylate has a low distribution quantity due to its relatively large molecular weight and high polarity (Vd). Hofmann's elimination of cisatracurium besylate is impacted by pH and temperature. Apart from atracurium besylate, cisatracurium besylate somehow doesn't appear to be degraded directly by ester hydrolysis. Hofmann elimination occurs in plasma and tissue and represents approximately 77 percent of total cisatracurium besylate elimination. In patients with normal organ function, cisatracurium besylate has a complete body clearance (CL) of 0.28 L/h/kg (4.7 ml/min/kg), a steady-state Vd of 0.145 L/kg, and an elimination half-life of 25 minutes(13).

2. In 2013, Ozlem Sagir, Funda Yucesoy Noyan, Muslum Cicek, and Huseyin Ilksen Toprak published a study to compare the effects of rocuronium, vecuronium, and cisatracurium on endotracheal intubation, extubation, and response time in geriatric people treated abdominal surgery, and they found that cisatracurium is safer in the elderly (5).

3. N. Shetti et al. concluded in a 2017 review article on cisatracurium besylate that Cisatracurium is a newer intermediate onset, duration skeletal muscle relaxant that can be used safely in hepatorenal impairment. It can be used in both elective surgical procedures under general anesthesia and in patients receiving prolonged controlled mechanical ventilation, with the only concern being cost-effectiveness (13).

4. Kasaby et al. (2012), especially in comparison 0.1mg/kg, 0.2mg/kg, and 0.3 mg/kg adult Cisatracurium doses to 0.5mg/kg atracurium doses throughout general anesthesia for abdominal surgery. They mentioned that atracurium is a much more efficient neuromuscular blocking agent than cisatracurium at the same dose (2ED95), whereas large doses of cisatracurium (4ED95 and 6ED95) offer greater effective, speedier neuromuscular blocking with prolonged duration of action, stable hemodynamic status, and no clinical characteristics associated with signs of histamine release (5).

5. In 2020, Wang X, Huang K, and colleagues will use a serial method to determine the best possible cis-atracurium dose for effective insertion of LMA. To twenty-three patients who undergo urinary surgery, the following cis-atracurium concentrations were administered serially: 150, 100, 70, 50, 30, and 20 gkg-1. The main finding was the way of responding to the insertion of a LMA with 16 points indicating "acceptable" responses and 16 points indicating "dissatisfying" responses. The median effective dose was calculated by averaging the seven fusions from "acceptable" and "dissatisfying" responses, as well as the ED50 of cis-atracurium for laryngeal mask airway insertion was determined to be 26.5 gkg-1 (8).

6. The effect of low dose ketamine and induction of cisatracurium on the intubating condition and prodromal time of cisatracurium was studied by Ahn BR, Kim SH, Yu BS et al in 2012. One hundred and twenty sequential patients were randomized categorized into 4 groups undergoing general anaesthesia. All subjects received a 5 ml injection of normal saline (group C), cisatracurium 0.01 mg/kg (group P), ketamine 0.5 mg/kg (group K), or a combined effect of cisatracurium 0.01 mg/kg and ketamine 0.5 mg/kg (group PK), abided by cisatracurium 0.15 mg/kg (groups C and K), and 0.14 mg/kg (group PK). The prodromal time of electromyographical reactions using single twitch and endotracheal intubation conditions was documented 60 seconds after cisatracurium administration, and the mixture of low-dose ketamine and cisatracurium priming was concluded to shorten the onset time and enhance endotracheal intubation conditions(14).

7. Jaime A. Foushee and colleagues published in 2015 during simulated Y-site administration, the physical suitability of cisatracurium with purchased was examined. 2.5-mL samples of calcium gluconate, diltiazem, esomeprazole, regular insulin, nicardipine, pantoprazole, and vasopressin were blended with either 2.5 mL of normal saline 0.9 percent (control) or 2.5 mL of cisatracurium to replicate a 1:1 Y-site ratio (experimental). Calcium gluconate, diltiazem hydrochloride, esomeprazole, regular insulin, nicardipine hydrochloride, and vasopressin demonstrated physical suitability with Cisatracurium during designed to simulate Y-site administering for 60 minutes. Due to a huge discrepancy in cloudiness between control and experimental samples, cisatracurium and pantoprazole should not be prescribed next to each other (15)

8. In 2011, SHAHRAM et al. performed an adult study with cisatracurium doses of 0.15mg/kg (3ED95), 0.20mg/kg (4ED95), and 0.25mg/kg (5ED95). They concluded that

0.20mg/kg (4ED95) and 0.25mg/kg (5ED95) cut the time required for endotracheal intubation while going to cause no major clinical changes in blood pressure or pulse rate and necessitating no intervention (11).

9. Kwon Ko et al. (2015) carried out a detailed study intubating conduction with propofol (2 mg/kg) prior to actually cisatracurium (0.2 mg/kg) and etomidate (0.3 mg/kg) prior to actually cisatracurium (0.2 mg/kg). They arrived at the conclusion that, when compared to propofol, Etomidate improves endotracheal intubation conditions and provides a quicker onset time of cisatracurium throughout anaesthetic induction (16).

Conclusion:

Cisatracurium is a relatively new intermediate-onset, long-lasting skeletal muscle relaxant. This medication can be used safely in patients with hepatorenal impairment. It, like other muscle relaxants, can be used in both elective surgical procedures performed under general anaesthesia and in patients undergoing prolonged controlled mechanical ventilation. The only concern could be the cost effectiveness in comparison to other skeletal muscle relaxants on the market.

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