NEON

PRODUCT MONOGRAPH

Cis-Artacil®

Cisatracurium Besylate Inj.

Beauty with Virtue

CISATRACURIUM BESYLATE INJECTION

Solution for Injection

5ml & 10ml vial (2mg/ml)

Dear Doctor,

We have come a long way from the South American Indians' arrow poisons (curare). The introduction of neuromuscular blockers in 1942 marked a major advance in anesthesia and surgery, allowing the anesthesiologist to maintain respiratory function during prolonged and complex surgery. Yet we are still far from the illusive 'ideal neuromuscular blocker'.

Neuromuscular blocking drugs are today routinely used during the administration of anesthesia to allow surgical access to body cavities without hindrance from voluntary or reflex muscle movement. Today, the neuromuscular blocking drugs are also used in the care of critically ill patients undergoing intensive therapy, to facilitate compliance with mechanical ventilation when sedoanalgesia alone have proved inadequate.

In keeping with tradition of bringing more useful agents to make your professional work in the operation room a little less stressful, Neon now brings you cisatracurium under the brand name of **CisArtacil**. This compilation of information on the molecule is done with the objective of presenting concise and clinically relevant useful information to help you decide the use of this molecule as appropriate in individual cases.

I am sure you will find this compilation informative and relevant to your practice.

With warm regards,
Dr Parimal Shah
Consultant Medical advisor
Neon Laboratories, Mumbai, India.

List of Abbreviations used

NMBA - NEUROMUSCULAR BLOCKING AGENTS
NDMR - NONDEPOLARIZING MUSCLE RELAXANT
TOF - TRAIN of FOUR
MEP - MOTOR EVOKED POTENTIAL
AQMS - ACUTE QUADRIPLEGIC MYOPATHY SYNDROME
ARDS - ACUTE RESPIRATORY DISTRESS SYNDROME
NMS - NEURO MUSCULAR JUNCTION
ASA - AMERICAN SOCIETY OF ANESTHESIOLOGISTS
AUC - AREA UNDER CURVE
CBF - CEREBRAL BLOOD FLOW
CL - CLEARANCE
Cmax - MAXIMUM CONCENTRATION
HR - HEART RATE
IM - INTRAMUSCULAR
IV - INTRAVENOUS
Kg - KILOGRAM
MAC - MINIMUM ALVEOLAR CONCENTRATION
MAP - MEAN ARTERIAL PRESSURE
mcg - Microgram
mg - miligram
min - minute
mcg/kg/h - Microgram/kilogram body weight/hour
mg/h - Milligram/hour
mmHg - mm of mercury
N_2O - Nitrous oxide
RR - Respiratory Rate
SBP - Systolic Blood Pressure
$T_{1/2}$ - half life
Vss - Volume of distribution at steady state

Contents

Cisatracurium

Introduction

Cisatracurium besilate (or besylate) is also known as BW-51W and BW-51W89. It is a benzylisoquinolinium neuromuscular blocker with an intermediate duration of action.[1] The other similar molecule available in our country is atracurium. The available preparation of atracurium is a mixture of 10 stereoisomers of which cisatracurium constitutes about 15%. Cisatracurium is a approximately five times more potent than the racemate mixture of atracurium.[1] Chemically, cisartracurium is R-cis, R'-cis isomer of atracurium besilate.[1] The word 'cisartracurium' is used to refer to this drug in the current compilation.

Mechanism of Action

Cisatracurium is a non-depolarising neuromuscular blocker. It acts by competitive antagonism. It binds with nicotinic acetyl choline receptors (nAChRs) on the motor end-plate of the neuromuscular junction (NMJ) to produce the neuromuscular blockade. The ED_{95} of cisatracurium (dose required to produce 95% suppression of twitch in response to nerve stimulation) is ~0.05 mg/kg in adults and children during N_2O/O_2/opioid anesthesia and 0.04 mg/kg during halothane N_2O/O_2 anesthesia in children.[1] It is also recently reported that NMBA cisatracurium is lung protective through its anti-inflammatory properties by blocking the nAChRα1 (nicotinic Acetyl Choline Receptor alpha 1).[2]

Pharmacodynamics

The degree and duration of neuromuscular blockade by cisatracurium increases and time to maximum neuromuscular block decreases in a dose-dependent manner. The time to maximum effect is delayed by approximately 1 minute in the elderly and in patients with renal failure, and shortened by almost 1 minute in patients with end-stage liver disease.[3] Clinical relationships exist among the time to onset of paralysis, neuromuscular blocker dosing, drug distribution, and ACh-receptor sensitivity. In a study that compared the time to 95% blockade at the adductor pollicis after administration of ED_{95} doses of succinylcholine, rocuronium, vecuronium, atracurium, mivacurium, and cisatracurium revealed that the most potent compound, cisatracurium, has the slowest onset and the least potent compound, rocuronium, has the most rapid onset.[3] Cisatracurium has a slightly longer onset time as compared to atracurium at equipotent doses. The onset of cisatracurium effect is slow to provide good conditions for intubation in less than 2 minutes after a dose twice the ED_{95}. This may be overcome by administration of $4xED_{95}$. The dose response relationships of select NMBA are given in **Table 1**.

The effective dose and the onset time were not significantly different between the adult and the elderly.[4]

Table 1: Dose-Response Relationships of Non-depolarizing Neuromuscular Blocking Drugs in Human Subjects[4]

Intermediate-Acting	ED_{50} (mg/kg)	ED_{90} (mg/kg)	ED_{95} (mg/kg)
Rocuronium	0.147 (0.069-0.220)	0.268 (0.200-0.419)	0.305 (0.257-0.521)
Vecuronium	0.027 (0.015-0.031)	0.042 (0.023-0.055)	0.043 (0.037-0.059)
Atracurium	0.12 (0.08-0.15)	0.18 (0.19-0.24)	0.21 (0.13-0.28)
Cisatracurium	0.026 (0.015-0.031)	--	0.04 (0.032-0.05)

Medians and ranges of reported values, ED_{50}, ED_{90} and ED_{95} are the doses of each drug that produce, respectively, a 50%, 90% and 95% decrease in the force of contraction or amplitude of the electromyogram of the adductor pollicis muscle after ulnar nerve stimulation.

Use of neostigmine for reversing shallow (defined as train-of-four ratio of 0.5) at different doses showed a dose of neostigmine 40 mcg/kg was the most effective (from a train-of-four ratio of 0.5 to 1.0) at reducing recovery time after neuromuscular blockade.[5]

Cisatracurium administration did not cause prolongation of corrected QT (QTc) interval during anesthetic induction for laryngeal mask airway insertion.[6]

The clinical duration of neuromuscular block (time from injection to 25% twitch recovery) varies between 33 and 45 minutes after cisatracurium 0.1 mg/kg ($2xED_{95}$) and is ~55 minutes after cisatracurium 0.15 mg/kg ($3xED_{95}$) during barbiturate/N_2O/O_2 or propofol/N_2O/O_2 anesthesia. Doubling the dose of cisatracurium from 0.1 to 0.2 mg/kg increases the clinical duration of effect by 16 to 23 minutes. Once started, recovery (5 to 95% or 25 to 75% recovery indices) is independent of dose over a range of 0.1 to 0.4 mg/kg. This recovery rate is unaffected by age, renal failure or end-stage liver disease, but appears to be slower following the use of sevoflurane in children. The recovery from the block with cisatracurium can be effectively accelerated by administration of an anticholinesterase agent once recovery has started. It offers a more predictable recovery profile than vecuronium after prolonged use in patients in intensive care. [1]

Atracurium may induce histamine release after rapid administration. However, cisatracurium is not associated with dose-related histamine release (at bolus doses of 5-8 x ED_{95}) and has demonstrated cardiovascular stability in both healthy patients and those with coronary artery disease (at 5-6 x ED_{95}). Cisatracurium has the least histamine-releasing effect at higher doses. No evidence of histamine release was seen after the administration of 0.15 mg/kg ($3xED_{95}$ for twitch depression) of cisatracurium to neurosurgical ICU patients.[7]

As compared to atracurium, cisatracurium is 3 times* as potent and has a more desirable adverse drug event profile, including lack of histamine release, minimal cardiovascular effects, and less interaction with autonomic ganglia. Though it too undergoes ester hydrolysis as well as Hofmann degradation, the plasma laudanosine concentrations after cisatracurium administration are five to ten times lower than those detected after atracurium administration. (Different published reports mention different relative potency of cisatracurium as compared to atracurium; the reported relative potency varies between 3 and 5. However, when compared on the basis of ED_{95} dose; the relative potency works out to 5 times and that is the figure generally followed in this compilation.)

The clinical profiles of a few muscle relaxants (some with steroid structure such as vecuronium and rocuronium) and the available benzylisoqunoliniums (atracurium and cisatracurium) are compared in **Table 2**.

Table 2: Hemodynamic Effects of Commonly Used Neuromuscular blocking agents[8]

Muscle Relaxants	HR	Contractility	SVR	Net Effect on BP
Vecuronium	↔	↔	↔	↔
Atracurium	↔	↔	↓	↓
Cisatracurium	**↔**	**↔**	**↔**	**↔**
Rocuronium	↔	↔	↔	↔
Succinylcholine	↑↓	↓	↔	↑↓

↔ = No or insignificant change, ↑ = Increase, ↓ = decrease, HR = Heart rate; SVR = Systemic vascular resistance; BP = Blood pressure

Cisatracurium offers two major advantages over atracurium.
A) It releases less histamine, and
B) Produces less laudanosine.
Being more potent than atracurium, fewer molecules are required to produce the same level of blockade, thus, less laudanosine is produced. Histamine release starts at $5\times ED_{95}$, but becomes clinically relevant from $8\times ED_{95}$. Commonly used intubating doses of cisatracurium range from 2 to $4\times ED_{95}$, offering a stable cardiovascular profile comparable to that of vecuronium.[9] Supratherapeutic dosing of cisatracurium ($8xED_{95}$) does not result in increased histamine production, resulting in a significantly improved adverse event profile. In neurosurgical mechanically ventilated patients, cisatracurium was superior over atracurium as measured by reduced intracranial pressure, cerebral perfusion, and lower overall blood pressure. Furthermore, lower dosing of cisatracurium results in the reduction of the amount of laudanosine, a major metabolite related to increased seizure events in animals.[12]

Pharmacodynamics in renal Failure

The effect of cisatracurium was compared in 15 healthy subjects and in 17 patients with chronic renal failure (CRF) using a bolus dose of 0.1 mg/kg ($2xED_{95}$). The mean ± SD creatinine clearance in the CRF patients was 823 ± 265 µmol/L as against 84 ± 16 µmol/L in the healthy adults. Fifteen patients with normal renal function were also investigated using an approximate equipotent dose of atracurium (0.4 mg/kg). Cisatracurium had an intermediate duration of action which was not significantly affected by the presence of chronic renal failure. In healthy patients, recovery from cisatracurium may take slightly longer than that after atracurium.[10]

Pharmacodynamics in Liver dysfunction

A recent study has reported that a $2 \times ED_{95}$ dose of cisatracurium is safe and effective choice of neuromuscular blocking agent for anesthesia for both adults and children with hepatic disease. It can also offer a favorable condition for endotracheal intubation. The onset was relatively shorter in infants than in adults, but the dosing interval was comparable to that in adults. After discontinuation, infant patients recovered faster than the adult patients.[11]

Effect of combination of NMBAs

A comparison of the dose-response relationships of individual and combinations of cisatracurium with atracurium, vecuronium, and rocuronium in humans (n=180 adults during nitrous oxide-fentanyl-propofol anesthesia) determined by probit analysis showed the calculated values were as per Figure 1.

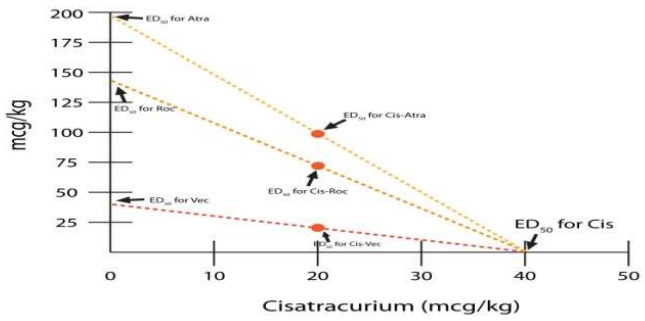

Figure 1: First-twitch ED_{50} isobologram for the interaction of cisatracurium (Cis) with atracurium (Atra), Rocuronium (Roc), and Vecuronium (Vec). The dashed line connecting the single drug ED_{50} points is the theoretical additive line; points on this line are the theoretical additive points (95%CI).

The experimentally determined ED_{50} dose of the cisatracurium-vecuronium (Cis-Vec) combination showed a significant synergistic effect ($p<0.0001$) and so did the experimentally determined ED_{50} dose of the cisatracurium-recuronium (Cis-Roc) combination ($p<0.0001$). The exact mechanisms of synergistic interaction are not known. Theoretical possibilities are many. It was concluded that the interaction between cisatracurium and vecuronium or rocuronium was found to be synergistic, but the interaction between cisatracurium and atracurium was found to be additive.[12] A study to investigate synergism between rocuronium and cisatracurium observed that a clinically effective combination of rocuronium and cisatracurium at doses 10% of the ED_{95} of respective drugs was sufficient to maintain neuromuscular relaxation during minor surgery.[13]

Hypersensitivity and cross reactivity.[14,15,16,17]

The mortality of allergic reactions during anesthesia is estimated to be 6%, and between 1 in 10000 and 1 in 1250 anesthetized patients die from such a reaction. Neuromuscular blocking agents (NMBAs) can behave as antigens. They are responsible for more than two-thirds of anaphylactic or anaphylactoid reactions and for 80% of cases of anaphylactic shock during anesthesia. The nondepolarizing muscle relaxant, cisatracurium, induces fewer allergic reactions than other NMBAs such as succinylcholine, whose administration entails a higher risk than most other commonly used agents.[12]

In a review of a 12 year survey at a French pediatric center, no sensitization to cisatracurium was observed. There were hypersensitivity reactions in 68 children. IgE-mediated anaphylaxis was diagnosed on skin test combined with the clinical history. The NMBA were responsible for 31 of the 51 IgE-mediated anaphylaxis (Figures 2 to 4). The high frequency of IgE-anaphylactic reactions and the feasibility of skin tests in children justify systematic allergy testing whenever a hypersensitivity reaction occurs during general anesthesia and can improve the safety of subsequent anesthetic procedures.[11]

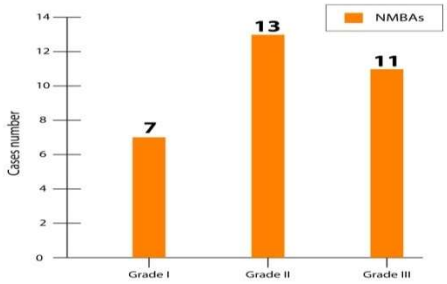

Figure 2: Frequency of non-IgE-mediated reactions and frequency of NMB agents with positive skin test according to the severity of the hypersensitivity reaction during anesthesia.
(31 out of 68 total children who had anaphylactic reaction during anesthesia).

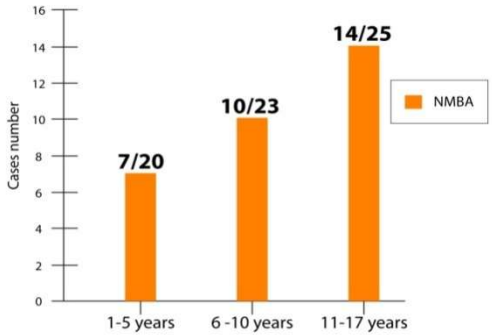

Figure 3: Number of positive skin tests according to age (n=number of children)

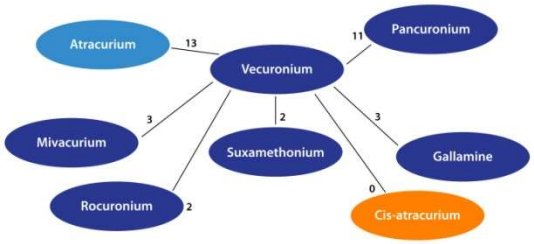

Figure 4: Cross-sensitization between neuromuscular blocking agents (30 children of the 31; Numbers indicate cross reactions observed).

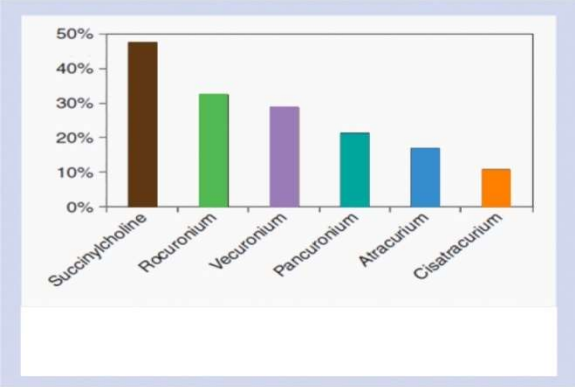

Figure 5: Percentage of cross-reactivity to individual NMB drugs.[13]

A study from Western Australia reviewing 10 year data ending on 31 December 2011 reported that during that period 80 patients were diagnosed with life threatening anaphylaxis to an NMBA. Rocuronium was responsible for 56% of cases of NMBD anaphylaxis, succinylcholine 21%, and vecuronium 11%. There was no difference in the severity of reactions for different NMBDs. The prevalence of cross-reactivity after NMBD anaphylaxis suggested that succinylcholine also has a high risk of triggering anaphylaxis. Cisatracurium had the lowest prevalence of cross-reactivity in patients with known anaphylaxis to rocuronium or vecuronium. The cross-reactivity results are shown in **figure 5**. For the allergy testing the dilution that may be used are shown in **Table 3**.

Table 3: Nonirritating test concentrations

Drug		SPT		IDT	
Drug name	**Undiluted Concentration (mg/ml)**	**Dilution**	**Maximum concentration (mg/ml)**	**Dilution**	**Maximum concentration (mg/ml)**
Atracurium	**10**	**1/10**	**1**	**1/1000**	**0.01**
Cis-atrcurium	**2**	**Undiluted**	**2**	**1/100**	**0.02**

IDT = intradermal test; SPT = skin prick test.

Authors of another study recommended that a systematic screening test for NMBAs or other anesthetic agents before anesthesia is not considered necessary even in patients with a history of allergy because they did not find allergy history associated with positive skin test for NMBAs.[18]

Pharmacokinetics

Cisatracurium volume of distribution is low due to its high molecular weight and high polarity. Cisatracurium undergoes Hofmann elimination which makes it a drug of choice in organ failure patients.[19] Cisatracurium acts within a few minutes after intravenous injection. Its salient parameters are compared with atracurium in Table 4. A comparison of pharmacokinetic and pharmacodynamic parameters of cisatracurium with those of atracurium and vecuronium are summarized in **Table 5.**

Table 4: Comparison of Cisatracurium with Atracurium[20,21]

IV Route	***Cisatracurium***	**Atracurium**
Onset Time – Approximate	***Slightly longer than 2 minutes***	~2 minutes
Duration of action	***15 to 35 minutes***	15 to 35 minutes
Plasma Protein Binding	***~ 80%***	~ 80%
Metabolism	***Hofmann elimination#***	Hofmann elimination#
Metabolites	***Laudanosine + Others***	Laudanosine + Others
Excretion Route of Laudanosine	***Urine & Bile***	Urine & Bile
Elimination half-life of Laudanosine*	***3-6 hours***	3-6 hours*
Elimination Half-life	***22 to 29 minutes. Slightly longer in elderly patients and in those with liver cirrhosis.***	20 minutes. Slightly longer in elderly patients and in those with liver cirrhosis
Placental transfer	***Crosses placenta (Insignificant amount)***	Crosses placenta *(Insignificant amount)*
Dependent on liver & / or kidney function	***Elimination is independent of renal and hepatic function***	Elimination is independent of renal and hepatic function
ED_{95}	***~0.05 mg/kg***	~0.25 mg/kg
Potency	***~ 5****	1
Histamine Release at clinical Doses	***None***	Yes

#Hofmann elimination is the major route of metabolism of cisatracurium and esterase route is a minor one; For atracurium Hofmann elimination is a minor route and esterase route is the major route of metabolism. *Laudanosine crosses the blood brain barrier and is dependent on the liver and kidney for its elimination. It accumulates in patients with impaired function of these organs. The amount of laudanosine produced is less with cisatracurium because of lower dose needed (due to its greater potency). ** Some reports mention the potency as 3x but as per ED_{95} dose it works out to be ~5x as potent as atracurium.

Table 5: Pharmacokinetic and Pharmacodynamic Parameters of Select Nondepolarizing Neuromuscular Blockers[1]

	Cisatracurium	**Atracurium**	**Vecuronium**
95% Effective dose (mg/kg)	**0.05**	0.25	0.05
Initial dose (mg/kg)	**0.1-0.2**	0.4-0.5	0.1
Half-life (min)	**22-31**	20	30-80
Infusion dose (mcg/kg/min)	**2.5-3.0**	4-12	1-2
% Renal excretion	**Hofmann elimination**	5-10 (Hofmann elimination)	50
Renal failure	**No change**	No change	↑Effect
% Biliary excretion	**Hofmann elimination**	Minimal	35-50
Hepatic failure	**Minimal to no change**	Minimal to no change	Mild effect
Active metabolites	**None**	None	3-desacetyl-vecuronium
Histamine hypotension	**None**	Dose-dependent	No
Vagal block tachycardia	**None**	No	No
Ganglionic block hypotension	**None**	Minimal to none	No
Prolonged block reported	**Rarely**	Rare	Yes (in ICU)

↑ = increased, ICU = Intensive Care Unit

A relationship exists between the time to onset of paralysis and neuromuscular blocker dosing, drug distribution, and ACh-receptor sensitivity. An important factor to consider is the volume of distribution (Vd), which may change as a result of disease processes. Cirrhotic liver disease and chronic renal failure often result in an increased Vd. Alterations in Vd affect both peak neuromuscular blocker serum concentrations and time to paralysis.[4]

Biotransformation

Hofmann elimination (a non-enzymatic breakdown that occurs at physiological pH and temperature) is the major route of metabolism and accounts for 77% of the total clearance of cisatracurium that degrades to form laudanosine and the corresponding monoquaternary acrylate (which in turn is broken down to a monoquaternary alcohol and then laudanosine).[17] There is also some ester hydrolysis by non-specific plasma

esterases. The metabolites have no neuromuscular blocking activity. Excretion of cisatracurium is in urine and bile, mostly as metabolites. [15] Although the liver and kidneys play a very small role in the excretion of cisatracurium, urinary and hepatic elimination are important for the metabolites of laudanosine. The apparent volume of distribution of cisatracurium at steady-state ranges from 0.11 to 0.16 L/kg in healthy adults (figures likely to be underestimates). Cisatracurium is cleared from the body at a rate of 0.27 to 0.34 L/h/kg, with an elimination half-life of 22 to 35 min.[1]

Liver/Kidney function impairment

Because renal excretion accounts for only 16% of the elimination of cisatracurium, renal failure should have little impact on its duration of action.[22] Clearance of the drug is slightly decreased (by 13%) in this patient population.[4] Cisatracurium produces and releases less laudanosine and histamine than atracurium. The cerebral effects of cisatracurium are essentially similar to or weaker than those of atracurium.[23] The volume of distribution (Vd) may change as a result of disease processes. Cirrhotic liver disease and chronic renal failure often result in an increased Vd and decreased plasma concentration for a given dose of water-soluble drugs. The alterations due to various hepatobiliary and renal disorders in the pharmacokinetic parameters of cisatracurium, atracurium, Vecuronium and rocuronium are compared in Tables 6 & 7.

Table 6: Pharmacokinetics of NMB Drugs in Patients with Normal Liver Function or Hepatobiliary Disease[4]

	Plasma Clearance (ml/kg/min)		Volume of Distribution (ml/kg)		Eliminate Half-life (min)		Hepatic Pathology
	Normal	**Disease**	**Normal**	**Disease**	**Normal**	**Disease**	
Atracurium	5.3	6.5	159	207*	21	22	Hepatorenal
	6.6	8.0*	202	282*	21	25	Cirrhosis
Cisatracurium	5.7	6.6*	161	195*	23.5	24.4	Transplantaion Related
Vecuronium	4.26	2.73*	246	253	58	848	Cirrhosis
	4.30	2.36*	247	206	58	98*	Cholestasis
	4.5	4.4	180	220	58	51	Cirrhosis
Rocuronium	2.79	2.41	184	234	87.5	96.0	Cirrhosis
	217	217	16.4	23.4*	76.4	111.5*	Mixed
	296	189	151	264*	56	98*	Cirrhosis
	3.70	2.66*	211	248	92	143*	Cirrhosis

**Significant difference between normal hepatic function and hepatobiliary disease*

Table 7 – Pharmacokinetics of Neuromuscular Blocking Drugs in Patients with Normal Renal Function or Renal Failure[4]

	Plasma Clearnace (ml/kg/min)		Volume of Distribution (ml/kg)		Elimination Half-life (min)	
	Normal Function	**Renal Failure**	**Normal Function**	**Renal Failure**	**Normal Function**	**Renal Failure**
Intermediate-Acting Drugs						
Atracurium	6.1	6.7	182	224	21	24
	5.5	5.8	153	141	19	20
	10.9	7.8	280	265	17.3	19.7
Cisatracurium	**5.2**	-	**31**	-	-	-
Vecuronium	3	2.5	194	239	78	97
	5.3	3.1*	199	241	53	83*
Rocuronium	2.9	2.9	207	264*	71	97*

*Significant difference between normal renal function and renal failure.

Pharmacokinetics in Sepsis

A study was carried out to characterize pharmacokinetics and pharmacodynamics of cisatracurium in intensive care patients with severe sepsis following a single bolus dose. The study suggested that standard dosing of cisatracurium in patients with severe sepsis results in a slower patient response with a reduced effect. The resistance to cisatracurium in these patients is more attributed to altered pharmacodynamics as pharmacokinetic parameters were similar to those described in other patient populations.[24] Neuromuscular block was assessed by peripheral nerve stimulation (ToF Watch). Steady-state volume of distribution was determined to be 111 ± 71 ml/kg and plasma clearance as 5.2 ± 1.8ml/min/kg in these patients with greater inter-patient variability compared with other populations. The study suggests that use of a larger dose may overcome delayed response. [24]

Pharmacokinetics when given as infusion

The parameters were compared with atracurium when given by bolus dose followed by continuous infusion in 20 healthy patients. Anaesthesia was induced with thiopentone, midazolam, fentanyl and 70% nitrous oxide in oxygen. Ten patients (Group C) were randomly allocated to receive cisatracurium 0.1 mg/kg and 10 patients (Group A) were given atracurium 0.5mg/kg. Neuromuscular block was monitored by mechanomyograph. When the first twitch of the train-of-four had recovered to 5% of control, an infusion of cisatracurium 3mcg/kg/min in Group C and of atracurium 10 mcg/kg/min in Group A, respectively, was started. The infusion rates were adjusted to maintain the first twitch of the train-of-four at 5% of control. No significant differences were found in recovery parameters between the two groups. Blood samples were taken at regular intervals following the bolus, during the infusion and for 8h thereafter. The plasma samples were analysed for cisatracurium and atracurium (method that distinguishes the three geometric isomer groups), laudanosine and monoquaternary alcohol. The different isomer groups of atracurium have different pharmacokinetics, the trans-trans group having the highest clearance (1440ml/min) and the cis-cis group the lowest (499ml/min). The clearance of cisatracurium (425 ml/min) is less than that of cis-cis atracurium and its elimination half-life is longer (34.9 min and 21.9 min, respectively as shown in Figure 6). The plasma concentration of laudanosine after cisatracurium was one-fifth of that after atracurium as shown in Figure 7.[25]

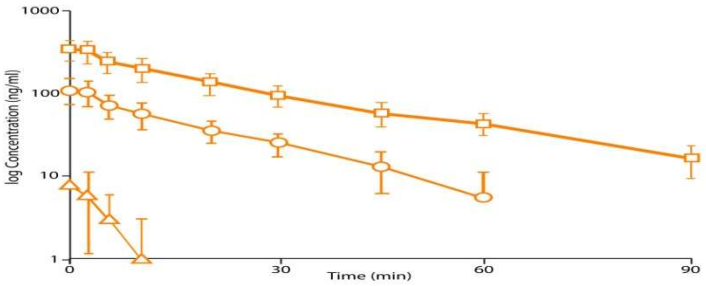

Figure 6: Mean plasma concentrations of the cis-cis (□), cis-trans (O) and trans-trans (Δ) isomer groups of atracurium after stopping the infusion at time zero. The last data point for the cis-cis isomer is from eight patients and the last data point for cis-trans atracurium is from seven patients. Error bars indicate 95% confidence intervals.

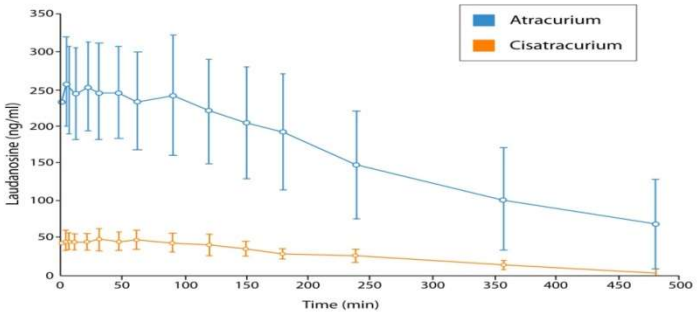

Figure 7: Mean plasma laudanosine concentrations in Groups C (cisatracurium, orange) and A (atracurium, blue) after stopping the infusion at time zero. Error bars indicate 95% confidence intervals.

Prolonged Infusion

In cases where prolonged administration of cisatracurium besylate is anticipated administration of cisatracurium via centrally placed venous catheters is preferable, or if that is not possible, a careful watch of respective peripheral intravenous sites is strongly recommended to diminish the risks of phlebitis and its associated complications or other cutaneous reactions.[29]

Pharmacokinetics after chemotherapy

In patients having undergone chemotherapy, the effect of NDMRs starts with a longer lag time and finishes earlier too. Thus, these patients are ready for intubation after a longer time. Moreover, cisatracurium injections need to be repeated at shorter intervals to maintain the desired level of blockade.[30]

Pharmacokinetics in the obese

Cisatracurium doses according to fat-free mass is clinically reasonable for inducing anesthesia in morbidly obese patients, but it is to be noted that due to a prolonged onset time, the timing of tracheal intubation would be delayed by 1-2 min.[31]

Pharmacokinetics in cardiac cases

Septal defects affect the pharmacokinetic profile of cisatracurium. Septal defects cause a marked increase in the distribution half-life and a significant delay in pharmacodynamic response. The onset time (i.e., the time to maximal neuromuscular block) gets prolonged from 2.2 minutes to 5.0 minutes due to poorer distribution.[32]

The pharmacokinetics and pharmacodynamics of cisatracurium were significantly altered in patients with severe mitral valve regurgitation (MR). The plasma concentration of the drug is higher in severe MR and the time to the maximal neuromuscular blocking effect of cisatracurium is delayed because the distribution rate of cisatracurium from the blood to the effect compartment is reduced in MR.[33]

Precautions

Temperature variation - Any lowering of body temperature is known to prolong the duration of action of cisatracurium by slowing its metabolism. Conversely there is a shortening of its activity or quality of action by enhanced metabolism when administered as an infusion at higher than body temperature. This correlation has been observed (raised

temperature of administred drug at 38°C via heated infusion channel) and significantly reduced neuromuscular blocking effect of cisatracurium.[34]

Age - It is been observed in a study that the clinical duration of neuromuscular blockade, effective action duration of neuromuscular blockade, and in vivo action duration of neuromuscular blockade were prolonged with increasing age; an observation that is consistent with earlier findings. Specifically, the duration of action of cisatracurium is positively correlated with age. One reason for this finding may be that the volume of distribution in infants is greater than that of adults. At present one can only state that age influences the neuromuscular blocking effects of cisatracurium to a certain extent.[35]

- Cirrhosis and advanced liver disease reduce the elimination of aminosteroidals (vecuronium, rocuronium, etc) and prolong the duration of blockade, especially after repeated doses or prolonged infusions. Cisatracurium and atracurium can be used without modification of dosing in such patients even with end-stage liver disease.[37]
- For patients with hepatic and renal dysfunction, cisatracurium is the drug of choice due to its independence from hepatic and renal metabolism. The duration of action of cisatracurium is similar in neonates as it is in children and adults.[9]
- The increased volume of distribution for some drugs observed in cirrhotic patients can also prolong the elimination half-life of pancuronium. In patients with end-stage liver disease cisatracurium elimination half-life and clinical durations of action remains similar to those in normal patients. Laudanosine, a metabolite of cisatracurium is eliminated primarily by the liver; and although its concentration may increase, because about five times less laudanosine is produced accumulation of this metabolite is not thought to be of any consequence in clinical practice.[22]
- Sugammadex is ineffective against succinylcholine, cisatracurium, and atracurium. Therefore, if neuromuscular blockade must be reestablished after using sugammadex, cisatracurium may be considered.[4]
- In the PICU cisatracurium 0.1 to 0.2 mg/kg followed by an infusion of 60 to 120 mcg/kg/h is often useful because its elimination is not dependent on renal or hepatic function.[24] The method of excretion of cisatracurium makes it particularly useful in newborns and children with liver or renal disease. If these drugs are given for more than a day, provision of regular drug holidays should be considered to avoid serum buildup of the drug and prolonged paralysis.[39]
- Because Hofmann degradation is the major route of metabolism of cisatracurium metabolism of cisatracurium is unaffected by disease or genetic variants of cholinesterase metabolism or in patients with pseudocholinesterase deficiency.[40]
- Cisatracurium offers advantages over atracurium because of higher potency and lack of histamine-release. [41]
- Cisatracurium use in elderly is advantageous because Hofmann degradation is unaffected by age. [42]
- In patients with chronic renal failure, the duration of action of cisatracurium is not prolonged. [4]
- In contrast with all other neuromuscular blockers, plasma clearance of cisatracurium is slightly increased in patients with liver disease (see Table 6 above).[4]
- Due to lack of histamine release with cisatracurium (but not with atracurium) administration is not likely to increased airway resistance and bronchospasm in patients with hyperactive airway disease.[4]
- Cisatracurium is cleared two to three times more rapidly than the long-acting drugs.[4]
- Abdominal muscle relaxation is essential for transplant procedures. Because of the duration of these cases, a continuous infusion of cisatracurium allows for titration of the level of block with reliable reversibility.[43]
- In patients with coronary artery disease, doses of ~6 x ED_{95} were not associated with a ~20% decrease in mean arterial pressure in any patient; the incidence of other hemodynamic changes did not differ between cisatracurium (0. 1 or 0.3 mg/kg) or vecuronium (0. 1 or 0.3 mg/kg) recipients. Cisatracurium at doses of ~8 x ED_{95} is not associated with dose-related changes in median plasma histamine levels.[1]

Drug Interaction

A large number of drugs may interact with NMBAs and affect the degree and/or duration of clinical effects through pharmacodynamic and pharmacokinetic interactions. The most relevant interactions with NMBA are summarized in table 8.

Table 8: Drug Interactions with Neuromuscular Blocking Agents

Therapeutic agent	Potential interaction
Aminoglycosides	Potentiate blockade
Tetracyclines	Potentiate blockade
Clindamycin and lincomycin	Potentiate blockade
Vancomycin	Potentiate blockade
Sedative/anesthetics	Potentiate blockade
Furosemide	Low doses: potentiate blockade; high doses: antagonize blockade
Beta-blockers	Potentiate blockade
Procainamide	Potentiate blockade
Quinidine	Potentiate blockade
Calcium channel blockers	Potentiate blockade
Methylxanthines	Antagonize blockade
Antiepileptic drugs	Acute: potentiate blockade; chronic: resistance to blockade
Carbamazepine	Resistance to blockade
Ranitidine	Antagonize blockade
Lithium	Potentiate blockade
Azathioprine	Mild antagonism; phosphodiesterase inhibition
Cyclosporin	Potentiate blockade
Corticosteroids	Potentiate steroid myopathy
Local anesthetics	Potentiate blockade

Note: Long-term anticonvulsant therapy with phenytoin, carbamazepine, or both is associated with resistance to the effect of nondepolarizing neuromuscular blockers, including pancuronium, vecuronium, cisatracurium, and rocuronium; but less so with atracurium. The etiology of this phenomenon is likely both pharmacodynamic and pharmacokinetic. [44]

The concurrent use of volatile general anesthetic agents, such as isoflurane, potentiate neuromuscular blockade when administered in high concentrations. The influence of anesthetic vapors on the effect of initial doses of NMBAs is minimal unless equilibration of anesthetic agent is allowed to occur before administration of the NMBA. More pronounced effects may be seen in the presence of sevoflurane and desflurane, which equilibrate more rapidly. Depending on the requirement for muscle relaxation during surgery, further doses of NMBA may not be required after the intubating dose. The volatile agent alone may produce sufficient muscle relaxation.[45]

A single dose of 8 mg of dexamethasone either as premedication 2 or 3 hours prior to surgery or just before induction of anesthesia hastens the onset and total recovery times of cisatracurium-induced block by approximately 15 and 9%, respectively.[46]

Advantages Of Cisatracurium

Why Cis-atracurium may be preferable over Atracurium

- Lack of histamine-release
- Less amount of laudanosine as metabolite
- Higher potency

More advantageous in renal dysfunction because

- No dose adjustment is needed
- Amount of laudanosine produced is less as compared to atrcacurium.
- Subject to more Hofmann degradation (80%) and less ester hydrolysis.

Clinical Potential

- A 4 x ED_{95} dose of cisatracurium (0.2 mg/kg) generally achieves good or excellent intubating conditions after 90 seconds in 95 to 100% of patients.[1]
- Literature suggests that in adults undergoing elective surgery, the mean infusion rate of cisatracurium required to maintain ~95% block ranges from 1.2 to 1.5 mcg/kg/min during N_2O/O_2/opioid or propofol anesthesia. Mean infusion rate required for children (aged 2 to 12 years) ranges between 1.6 and 1.8 mcg/kg/min. The 25 to 75% recovery index ranges from 15 to 18 min in adults and 11 or 14 min in children after a continuous infusion of cisatracurium.[1]
- For adult patients in intensive care, the mean infusion rate of cisatracurium required to maintain adequate neuromuscular block ranges between 2.6 and 3.2 mcg/kg/min. The mean time to 70% recovery of the ratio of the fourth to the first train-of-four response after infusion duration of at least 12 hours is significantly shorter with cisatracurium than with vecuronium (68 *vs* 387 minutes).[1]

Thus, the clinical potential may be summarized as:

- Facilitating intubation (**I**ntubation)
- During surgery (**S**urgery)
- Use in intensive care unit (**I**CU).

The clinical experience is therefore compiled under these three headings, and includes all age groups of patients.

A Note On Monitoring of NMBAs

The current guidelines recommend the routine monitoring of depth of neuromuscular blockade in all patients including the critically ill. Because the NMBAs have no analgesic and sedative effect a careful monitoring of the patients for signs of inadequate sedation or analgesia while receiving NMBAs is very important. The modality of choice to monitor the depth of nondepolarizing neuromuscular blockade is train-of-four (ToF) monitoring. To obtain the ToF ratio, the amplitude of the fourth response is divided by the amplitude of the first response. Before administration of a nondepolarizing muscle relaxant, all four responses are ideally the same: the ToF ratio is 1 to 1. During a partial nondepolarizing block, the ratio decreases (fades) and is inversely proportional to the degree of blockade. Several studies clearly demonstrate that airway protection and control have not recovered until a train-of-four (ToF) ratio of 0.9 has been achieved. Ventilatory response to hypoxia is also impaired during residual neuromuscular block via direct inhibition of chemoreceptor activity in the carotid bodies. Moreover, the reduced ability to control the jaw and tongue may interfere with airway patency and protection, even in individuals without impaired consciousness. Monitoring is particularly indicated in all patients undergoing long surgical procedures, in patients in whom blockade may be prolonged (neuromuscular diseases) or in whom reversal is intentionally avoided, and when drug interaction is suspected.[9]

Clinical Experience

Intubation

All of the available neuromuscular blocking agents have been used to produce adequate intubating conditions and relaxation during CABG surgery. Those used more frequently are compared with cisatracurium in Table 9.

Table 9: Nondepolarizing Neuromuscular Blocking Agents in Cardiac Anesthesia[47]

Relaxant	Intubating Dose (mg/kg)	Maintenance	Clinical Duration (min)	Hemodynamic effects	Special considerations
Pancuronium	0.08-0.12	0.01mg/kg q 20-60 min	60-120	Vagolytic ++ at clinical dosages, releases norepinephrine	Reduce dose or avoid completely in renal insufficiency
Vecuronium	0.08-0.2	0.8-2 µg /kg/h	45-90	Insignificant	Accumulation of active metabolite with long term use
Cisatracurium	**0.15 – 0.2**	**1-2 µg /kg/min**	**40-75**	**Insignificant**	**Mainly Hoffman elimination**
Rocuronium	0.4-1.0	0.01 mg/kg/min	35-75	Mildly vagolytic (high dosage)	No active metabolites

Literature reports-1

Cisatracurium was assessed with respect to intubating conditions during nitrous oxide-propofol-isoflurane anesthesia. Intubating conditions at 2 min were acceptable in 67% of patients following a dose of 0.1 mg/kg, and in 90% of patients following a dose of 0.15 mg/kg. Intubating conditions at 1.5 min were acceptable in 76% of patients even at a dose of 0.2 mg/kg. In comparison, intubating conditions at 2 min were acceptable in 95% of patients following 0.5 mg/kg of atracurium. Compared to 2 out of the 19 patients who had cutaneous flushing following the administration of atracurium there was no histamine release in the cisatracurium group. **The results suggest cisatracurium provides acceptable intubating conditions at 2 min following a dose of 0.15 mg/kg (Table 10, Figure 8).[48] The only possible disadvantage with cisatracurium (slow onset of effect to provide good conditions for intubation in < 2 minutes) may be overcome by giving a dose 4xED95 as shown by this study.**

Table 10: Comparison of intubating conditions at different dose of cisatracurium

Intubating condition	%	at dose of C	Urticaria
at 2 min acceptable	67%	0.10 mg/kg	
	90%	0.15 mg/kg	
At 1.5 min	76%	0.20 mg/kg	
		at dose of A	
at 2 min acceptable	95%	0.50 mg/kg	2 of 19

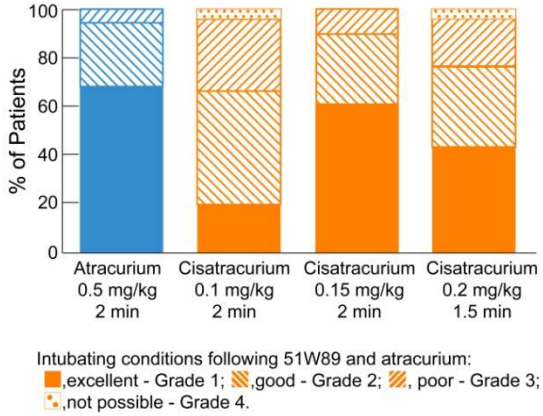

Figure 8: Comparison of intubating conditions at different dose of cisatracurium

Literature reports-2

In another study, tracheal intubation conditions produced by cisatracurium following induction of anesthesia with fentanyl (2 mcg/kg) and thiopentone (6 mg/kg) were observed. Sixty patients were randomly assigned to receive cisatracurium in a single bolus dose of either 0.15 or 0.20 mg/kg. Tracheal intubation was commenced 120 s after injection of the relaxant. The mean time taken to achieve intubation was significantly shorter in the 0.20 mg/kg group (137 s) than the 0.15 mg/kg group (149 s; $p < 0.05$). The intubating conditions were better after the larger dose. The results suggest that with thiopentone induced anesthesia, a dose of 0.20 mg/kg of cisatracurium is needed to ensure satisfactory intubating conditions as depicted in Table 11 & Figure 9. **Good to excellent conditions were present at 2 min in 97 % of patients after a dose of 0.2 mg/kg of cisatracurium.**[49]

Table 11: Physical characteristics, intubation scores after cisatracurium at the doses shown. Values are mean where appropriate.

	0.15 mg/kg	0.20 mg/kg
Intubating times;	149(42)	137(16)*
Intubating score:		
Excellent	8	19*
Good	16	10*
Poor	6	1*
Impossible	0	0

* P < 0.05 compared to Cisatracurium 0.15 mg/Kg

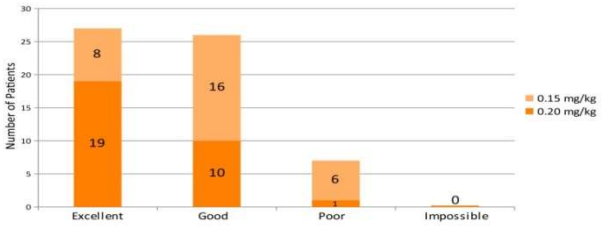

Figure 9: Tracheal intubation conditions by cisatracurium with induction of anesthesia using fentanyl (2 mcg/kg) & thiopentone (6 mg/kg)

Literature reports-3

Cisatracurium is approximately five times more potent than atracurium. Two equipotent doses of atracurium and cisatracurium were compared in children (2 to 12 y) for the quality of neuromuscular blockade, the intubation conditions and the side-effects. Eighty-four children (ASA I or ASA II) randomly received either 0.5 mg/kg atracurium (group A, n = 42) or 0.1 mg/kg cisatracurium (group C, n = 42). In both groups anesthesia was induced with identical doses & agents. The onset time, duration of effect, recovery index and the recovery time at ToF ratio of 0.7 are shown here in Figure 10.

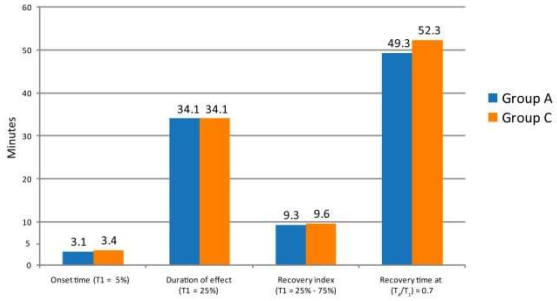

Figure 10: Comparison of the onset time, duration of effect, recovery index and the recovery time at ToF ratio of 0.7 in children given equipotent doses of atracurium and cisatracurium.

Cisatracurium and atracurium lead to comparable neuromuscular effects in children aged between 2 and 12 years. Only the intubation conditions may be better after atracurium, but that is followed by urticaria more often than cisatracurium.

Pretreatment with 0.02 mg/kg cisatracurium given 5 minutes before succinylcholine injection can alleviate succinylcholine-induced fasciculations without influence on muscle relaxation effects or endotracheal intubating conditions.[50]

Surgery

Many anesthesiologists prefer to use a nondepolarizing agent. Cisatracurium is not associated with histamine-mediated hypotension unlike atracurium. Pancuronium, on the other hand, may cause tachycardia and hypertension, although this effect may be attenuated by the simultaneous administration of synthetic narcotics such as fentanyl. Vecuronium is associated with hemodynamic stability. Rocuronium, given at 1.2 mg/kg, is similar in onset time to succinylcholine and may be the nondepolarizing muscle relaxant of choice in neurosurgical anesthesia. Overall, the choice of muscle relaxant depends on the anesthesiologist's preference as well as the nature of other drugs being administered at the time of induction. For subsequent neuromuscular blockade, any of the nondepolarizing agents can be used. If neurophysiologic monitoring (specifically motor evoked potential [MEP]) is employed, subsequent doses of muscle relaxants may impede adequate monitoring. Cisatracurium produces and releases less laudanosine than atracurium. The cerebral effects of cisatracurium are essentially similar to or weaker than those of atracurium. [23]

An important observation is that in patients with coronary artery disease, doses of ~6 x ED_{95} were not associated with a ~20% decrease in mean arterial pressure in any patient; the incidence of other hemodynamic changes did not differ between cisatracurium (0. 1 or 0.3 mg/kg) or vecuronium (0. 1 or 0.3 mg/kg) recipients. Cisatracurium at doses of up to ~8 x ED_{95} is not associated with dose-related changes in median plasma histamine levels.[1]

Maintenance of relaxation by continuous infusion is useful to keep relaxation smooth and to rapidly adjust the depth of relaxation to surgical needs. The infusion dosage is usually based on the dosage required to maintain 90-95% twitch inhibition under N2O/O2 with cisatracurium 1-2 µg/kg/min. The infusion dosage is decreased by approximately 30-50% in the presence of potent inhaled anesthetic. Infusions are typically employed for prolonged procedures or where patient movement might prove disastrous (e.g., some neurosurgical procedures). Continuous infusion is initiated only after the spontaneous recovery from an intubating dose. Upon reaching the desired level of neuromuscular block, the infusion must be individualized for each patient. Reliability of recovery is critical with infusions to avoid prolonged block.[11] A word of caution. It has been suggested that prolonged administration of cisatracurium besylate be only via centrally placed venous catheters or if that is not possible; to carefully monitor relevant peripheral intravenous sites to diminish the risks of phlebitis and associated complications, or other cutaneous reactions.[51]

Literature reports-4

The neuromuscular blocking effects and the reversibility of cisatracurium 0.1 or 0.15 mg/kg were compared with those of atracurium 0.5mg/kg during anesthesia with propofol, nitrous oxide and isoflurane. The intubating conditions are shown in Figure 11 and Table 12. The block was monitored by train-of-four stimulation response of the adductor pollicis muscle. The block was either allowed to recover spontaneously or was antagonized with neostigmine 50 mcg/kg at 10% or 25% recovery of the first twitch of the train-of-four. The median times to maximum block following cisatracurium 0.1 and 0.15 mg/kg and atracurium 0.5 mg/kg, respectively are shown in Table 13. The median time to recovery of the train-of-four ratio to 0.8 from different points, whether spontaneously or after reversal with neostigmine is also shown (Table 14). Administration of neostigmine significantly shortened the time to adequate recovery for both drugs and there were no differences between both the groups of patients given neostigmine at 10 or 25% recovery of the first twitch of the train-of-four. [34]

Table 12: Intubating conditions

	n	Excellent	Good	Poor
Cisatracurium 0.1mg/kg	30	5 (17%)*	17 (56%)	8 (27%)
Cisatracurium 0.15mg/kg	30	16 (54%)	10 (33%)	4 (13%)
Atracurium 0.5mg/kg	30	18 (60%)	12 (40%)	0†

*p<0.05vs.cisatracurium 0.15mg/kg and atracurium 0.5mg/kg.†p<0.05 vs. cisatracurium 0.1mg/kg and cisatracurium 0.15mg/kg.

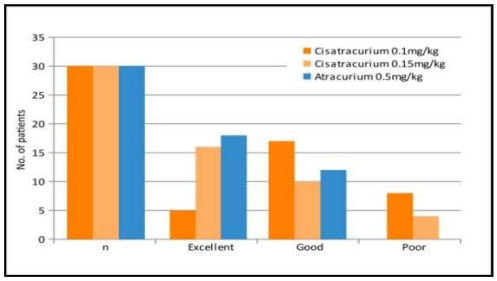

Figure 11: Comparison of Intubating Conditions at two different doses of Cisatracurium

Table 13: Lag time (time to start of identifiable block) and onset time (time to maximum block). Values are given as median (range). [34]

	n	Lag time; min	Onset time; min	Maximum Suppression of T1 ; %
Cisatracurium 0.1mg/kg	30	0.8 (0.5-1.0)	2.7 (1.9-4.1)	100
Cisatracurium 0.15mg/kg	30	0.8 (0.5-1.1)	2.2 (1.5-4.5)*	100
Atracurium 0.5mg/kg	30	0.6 (0.4-0.8)†	1.5 (1.1-2.7)†	100

*p<0.05 vs.cisatracurium 0.1mg/kg. †p<0.001 vs. cisatracurium 0.1mg/kg and cisatracurium 0.15mg/kg

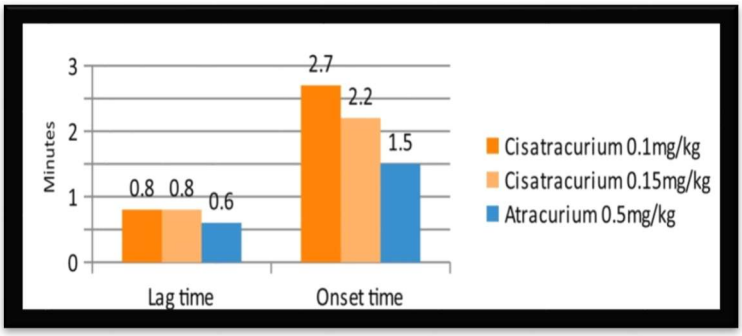

Figure 12: Comparison of Lag time and maximum suppression after two different doses of Cisatracurium

Table 14: Recovery times (min). Values are given as median (range).[34]

		Time from administration neuromuscular blocking drug to			Time from administration of neostigmine to	
Drug & dose	Reversal	T_1=25%	T_1= 90%	ToF=0.8	T_1=90%	ToF=0.8
Cisatracurium 0.1mg/kg	spontaneous	48(40.2-55.4)	65(50.9-73.8)	74(62.8-86.6)		
Cisatracurium 0.1mg/kg	T_1=10%	39(34.7-50.6)	43(41.0-58.0)†	48(42.8-60.8)‡	7.9(4.4-9.5)¶	11.6(5.8-14.0)§
Cisatracurium 0.1mg/kg	T_1 = 25%	45(37.2-52.7)	48(40.1-56.1)†	50(42.9-58.0)‡	3.4(2.3-4.5)	5.4(3.2-9.0)
Cisatracurium 0.15mg/kg	spontaneous	59(43.8-68.3)	74(57.4-96.5)	90(65.5-106.7)		
Cisatracurium 0.15mg/kg	T_1 = 10%	54(33.6-63.4)	61(38.4-70.0)	66(41.5-72.7)	6.4(4.1-15.2)¶	9.8(5.4-18.6)
Cisatracurium 0.15mg/kg	T_1=25%	51(41.0-61.4)	55(44.1-67.9)*	57(49.8-71.3)*	3.2(2.1-6.5)	5.2(3.8-13.3)
Atracurium 0.5mg/kg	spontaneous	47(34.0-57.0)	63(48.6-75.0)	75(59.6-90.5)		
Atracurium 0.5mg/kg	T_1=10%	45(35.7-51.5)	52(39.0-58.4)	56(42.4-65.5)*	6.7(4.0-10.0)	9.3(4.4-18.6)
Atracurium 0.5mg/kg	T_1 = 25%	48(39.4-52.8)	52(45.2-57.0)	54(45.6-61.1)*	3.6(2.0-6.5)	5.9(3.4-8.6)

*p<0.05vs.spontaneous.†p<0.01vs.spontaneous.‡p<0.001vs.spontaneous.§p<0.05vs.reversalatT1=25%.¶p<0.01vs.reversal at T1=25%.

The results of the study show that **the block produced by cisatracurium can be antagonised by neostigmine as easily as that produced by atracurium.** The overall times to adequate antagonism are similar for the equipotent doses whether the block is reversed from a T_1 value of 10% or 25% (Figure 13). The longer total time between the administration of cisatracurium 0.15mg/kg and adequate reversal after this dose is due to the longer time taken for spontaneous recovery of T_1-10% or 25%.[52]

Literature reports-5

The study mentioned under pharmacokinetics after infusion also performed clinical evaluation as regards the onset and recovery after the bolus dose followed by continuous infusion in 20 healthy patients. Anaesthesia was induced with thiopentone, midazolam, fentanyl and 70% nitrous oxide in oxygen. Ten patients (Group C) were randomly allocated to receive cisatracurium 0.1 mg/kg and 10 patients (Group A) were given atracurium 0.5mg/kg. Neuromuscular block was monitored by mechanomyograph. When the first twitch of the train-of-four had recovered to 5% of control, an infusion of cisatracurium 3 mcg/kg/min in Group C and of atracurium 10 mcg/kg/min in Group A, respectively, was started. The infusion rates were adjusted to maintain the first twitch of the train-of-four at 5% of control. The times to 90% and maximum depression of the first twitch of the train- of-four were significantly longer after cisatracurium than atracurium (2.2 and 3.4 min compared with 1.3 and 1.8 min, respectively; $p < 0.01$ in each instance, Table 15). No significant differences were found in recovery parameters between the two groups.[25]

Table 15: Comparison of the times to NM block after bolus and infusion and time to recovery after cisatracurium 0.1mg/kg followed by infusion of cisatracurium 3mcg/kg/min and of atracurium 0.5mg/kg/min followed by infusion of atracurium 10 mcg/kg/min, respectively[20]

	Cisatracurium	Atracurium
Onset		
Time to 90% depression of T_1/T_0; min	2.3 (0.4) [1.7-2.7]	1.3 (0.2) [0.8-1.6]*
Time to 95% depression of $T_1=T_0$; min	2.4 (0.4) [1.7-2.9]	1.5 (0.3) [0.8-1.8]*
Time to maximum depression of T_1/T_0; min	3.6 (0.9) [2.1-5.0]	1.8 (0.4) [1.0-2.3]*
Maximum depression of T_1/T_0; %	100	100
Recovery after bolus		
Time to 5% recovery of T_1/T_0; min	37.1 (5.9) [29.7-44.0]	41.6 (5.9) [36.0-52.0]
During infusion		
Minimum depression of T_1/T_0; %	90 (4.0) [85-96]	85 (8.0) [67-93]
Maximum depression of T_1/T_0; %	98 (1.0) [96-100]	97 (2.0) [94-100]
Recovery after infusion		
Time to 25% recovery of T_1/T_0; min	16.3 (10.1) [6.5-42.5]	14.2 (11.0) [0.0-37.2]
Recovery index: (25-75%); min	15.9 (5.2) [10.0-25.7]	17.3 (6.9) [11.6-43.9]
Time to ToF ratio= 0.7; min	40.7 (14.1) [27.8-76.4]	40.0 (17.0) [23.1-79.2]

*p<0.01.

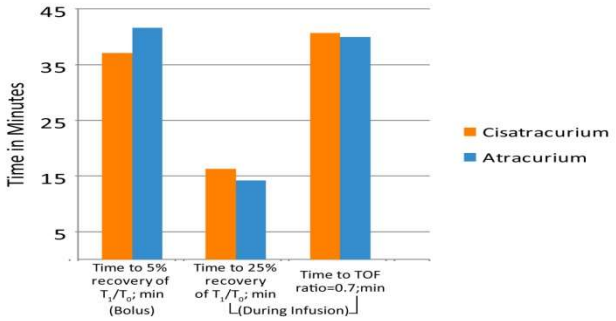

Figure 13: Comparison of Recovery times after bolus dose and continuous infusion of Cisatracurium and atracurium

The times to 90% and maximum depression of the first twitch of the train- of-four were significantly longer after cisatracurium than atracurium (Figure 13). No significant differences were found in recovery parameters between the two groups.

Literature reports-6

Neuromuscular blocking drugs exhibit different degrees of fade in response to train-of-four (ToF) stimulation and represent their relative prejunctional effects. This study was designed to compare the ToF fade after cisatracurium and compare it with other muscle relaxants. ToF fade during onset and recovery of block were recorded after administration of cisatracurium 0.05 or 0.1 mg/kg, atracurium 0.5 mg/kg, vecuronium 0.08 mg/kg, or rocuronium 0.6 mg/kg to patients anesthetized with fentanyl, nitrous oxide and a propofol infusion. **ToF fade during onset of block was greater with the lower dose of cisatracurium compared with the higher dose of cisatracurium and all other relaxants. ToF fade during recovery was similar.** The median times and ranges for the onset of maximum block and for the recovery of T_1 to 25% of control and to a ToF ratio of 0.8 were as shown below (Tables 16, Figure 14).[53]

Table 16. Onset and recovery (in min) of neuromuscular block; median (range)

	n	Time to maximum block	Time to recovery of T1 to 25%	Time to recovery of ToF ratio of 0.8
Cisatracurium 0.1mg/kg	14	3.4 (2.1-5.6)*	41 (20.6-50.0)[a]	65 (39.6-77.7)
Atracurium 0.5 mg/kg	15	1.5(1.2-2.3)	43(37.0-53.7)[b]	69 (58.0-79.4)
Vecuronium 0.08mg/kg	13	2.0(1.5-2.7)	31(23.0-46.4)	60(45.4-116.9)
Rocuronium 0.6mg/kg	15	1.0(0.7-1.3)**	33(18.1-57.3)	50(28.4-76.1)[b]

*p<0.01 vs.atracurium and rocuronium; **p<0.01 vs. mivacurium and vecuronium; †p<0.01vs.all other groups; [a] n = 13, [b] n=14

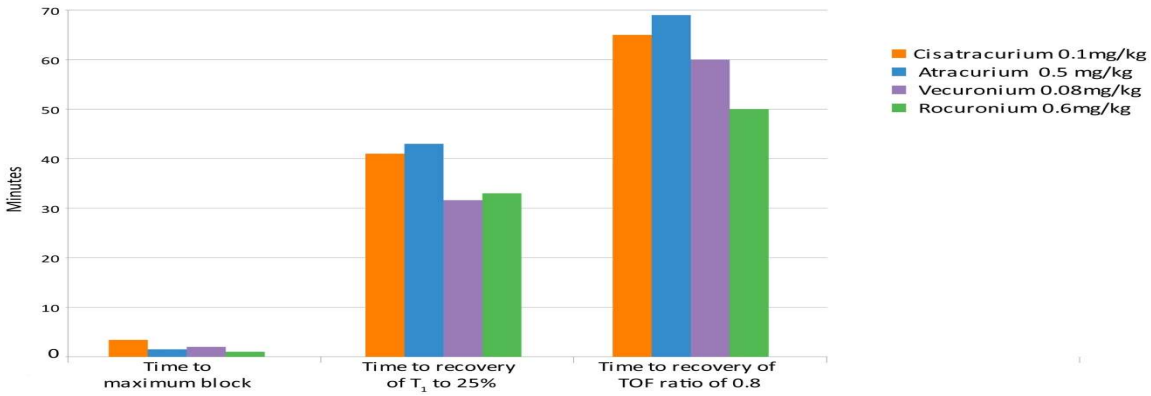

Figure 14: Onset and recovery (in min) of neuromuscular block

Literature reports-7

The neuromuscular and cardiovascular effects of a single, rapidly administered intravenous dose of cisatracurium 0.15 mg/kg were studied in 27 infants (aged 1±23 months) and 24 children (aged 2±12.5 years). After midazolam premedication, anaesthesia was induced and maintained with thiopental and alfentanil in addition to nitrous oxide in oxygen. Neuromuscular function was monitored by evoked adductor pollicis electromyography. At least 15 min after intubation, each patient received cisatracurium 0.15 mg/kg over 5 s. Complete neuromuscular blockade was produced by this dose in all but one infant. The mean (SD) onset time of maximal blockade was more rapid in infants [2.0 (0.8) min] than in children [3.0 (1.2) min], p=0.0011. The clinical duration of action of cisatracurium (recovery of evoked response to 25% of control) was significantly longer in infants [43.3 (6.2) min] than in children [36.0 (5.4) min], p <0.0001. Once neuromuscular function started to recover, the rate of recovery was similar in both age groups (Table 17). **Changes in blood pressure and heart rate after the administration of cisatracurium were negligible in both age groups. Cisatracurium, at a dose of 0.15 mg/kg, was effective and well tolerated in infants and children.**[54]

Table 17: Neuromuscular effect of cisatracurium0.15mg/kg during nitrous oxide–opiod anaesthesia.
Values are mean (SD) [range]

	Infants	Children	P
Maximum T_1 suppression;%	99.0(3.1) [85-100]	100 (0)	ns
Onset times; min			
90% block	1.5 (0.5) [0.7-3.2]	2.1 (0.4) [1.3-2.8]	0.0001
Maximum block	2.0(0.8)[1.3-4.3]	3.0 (1.2) [1.5-8.0]	0.0011
Recovery times; min			
T_1 = 5%	36.2 (6.0) [27.7-49.8]	28.6 (5.4) [18.8-38.3]	<0.0001
T_1 = 25%	43.3 (6.2) [34.2-57.7]	36.0 (5.4) [28.5-45.8]	<0.0001
T_1 = 75%	55.0 (7.3) [45-7.17]	47.1 (6.0) [38-61.7]	<0.0001
T_1= 95%	64.8(7.9) [53.5-84]	55.0 (7.0) [45-71.8]	<0.0001
Train - of-four ratio = 0.7	59.2 (6.8) [48.8-75.5]	53.7(6.5) [43.5-65.8]	0.0049
Recovery index; min			
25-75%	11.7 (2.7) (7.3-18.3]	11.1 (2.1) [8.5-17.7]	ns
5-95%	28.4 (4.8) [21-38]	26.3 (4.0) [20.8-36.5]	ns

Ns- not significant

Literature reports-8

Average EMG amplitude and the positive rate of effective EMG amplitude of cisatracurium besylate are all higher than those of vecuronium bromide. With faster effects and shorter action time, cisatracurium besylate is more suitable in thyroid surgery for intraoperative neurophysiological monitoring.[55]

Other Medical Reports

For spinal surgery of elderly patients, closed-loop target controlled infusion of cisatracurium was superior to continuous infusion and intravenous injection. The time of muscle relaxation recovery was shortened, the dosage of cisatracurium was reduced, and the number of cases of insufficient muscle relaxation was reduced.[56]

In patients with heart disease whose ejection fraction reported by echocardiography or cardiac catheterization is 35% or less before the open heart surgery; cisatracurium as the muscle relaxant, is advantageous and better.[57]

It is reported that during laparoscopic cholecystectomy, the injection of the ED_{95} of rocuronium and cisatracurium can provide a more suitable muscle relaxation effect than the injection of intubating doses of rocuronium or cisatracurium alone.[58]

Use in Intensive care

Note of caution for use of *any* NMBA in ICU.

Most of the recommendations regarding the use of these drugs in intensive care units are extrapolated from short-term studies in relatively healthy patients undergoing surgery. This explains the reports of prolonged weakness after long-term (>24-hour) use of NMBAs in critically ill patients. Many of these drugs (such as vecuronium & pancuronium) are biotransformed to active metabolites. In critically ill patients with creatinine clearance of <50 ml/min, the recovery time is prolonged after the administration of infusions of vecuronium. This prolonged time to recovery may be related to effects of the blocking drug that are pharmacologic (drug overdoses or accumulations of active metabolites), physiologic (changes in the neuromuscular junction with critical illness), or potentially toxic (effects that are secondary to drug–drug interactions or to drug–muscle or drug–nerve interactions).[59] Long-term administration of neuromuscular blocking agents, particularly those such as vecuronium with a steroid structure, has been associated with persistent paralysis. The metabolite 3-desacetylvecuronium, which rarely is seen in patients with normal renal function but is quite common in patients with delayed recovery may be the culprit. However, prolonged paralysis also can be seen after

treatment with other drugs such as pancuronium and cisatracurium, which do not necessarily share the same structure or have persistent metabolism. It is suspected that neurogenic atrophy occurs with prolonged paralysis resulting in a flaccid quadriplegia or more localized weakness of respiratory muscles.[60] **The recovery time is much less after infusions of cisatracurium.** A list of recommendations is given in Table 18.

Although several NMBAs are available, the drugs most commonly used in the ICU are the aminosteroid compounds (e.g., rocuronium) and the benzylisoquinolinium compounds (e.g., cisatracurium). Because these drugs are infused continuously, the duration of action is not as important as if they were given as a single bolus, but duration of action does become of consequence when it is discontinued and the physician is assessing the return of the patient's neuromuscular function. The objective is to strive to achieve a ToF of one or two twitches. If no twitches are observed, the patient may have received an overdose of medication and may be at risk for development of acute quadriplegic myopathy syndrome (AQMS), a situation that develops in patients receiving NMBAs in which, when the medication is discontinued, the patient remains flaccid for much longer than would be predicted simply based on the pharmacokinetics of the medications that were infused. Bolus administration of NMBAs, when tolerated, is advantageous for monitoring the effects of sedation and analgesia, as well as decreasing the incidence of tachyphylaxis.[61] An algorithm (Figure 16) often helps the clinician decide regarding the use of NMBA in a particular case. Keep in mind that **as compared with vecuronium, cisatracurium is associated with a significantly faster and a more predictable recovery after continuous infusion in patients in intensive care**. [3] A word of caution. It has been suggested that prolonged administration of cisatracurium besylate be only via centrally placed venous catheters or if not possible; to careful monitor relevant peripheral intravenous sites to diminish the risks of phlebitis and associated complications or other cutaneous reactions.[62]

Recommendations for ICU Patients

Table 18: Recommendations for Administration of (NMBAs) to ICU Patients

- Use and document a standardized approach for administering and monitoring NMBA
- Use NMBA only after optimizing ventilator settings and sedative and analgesic medication
- Establish the indications and clinical goals of neuromuscular blockade, and evaluate at least daily
- Select the best NMBA on the basis of patient characteristics:
    - Use intermittent NMBA therapy with pancuronium or other suitable agent if clinical goals can be met.
    - If continuous infusion is required and renal or hepatic dysfunction is present, select atracurium or cisatracurium, and avoid vecuronium.
- Use the lowest effective dose for the shortest possible time (< 48 h if possible), particularly if corticosteroids are concomitantly administered.
- Administer adequate analgesic and/or sedative medication during neuromuscular blockade, and monitor clinically.
- Anticipate and prevent complications, including provision of eye care, careful positioning, physical therapy, and deep vein thrombosis (DVT) prophylaxis.
- Avoid the use of medications that affect NMBA actions. Promptly recognize and manage conditions that affect NMBA actions.
- Adjust NMBA dosage to achieve clinical goals (i.e., patient–ventilator synchrony, apnea, or complete paralysis).
- Periodically (i.e., at least once or twice daily) perform NMBA dosage reduction, and preferably cessation (drug holiday) if clinically tolerated, to determine whether neuromuscular blockade is still needed and to perform physical and neurologic examination.
- Periodically perform and document a clinical assessment in which spontaneous respiration, as well as limb movement, and/or the presence of deep tendon reflexes (DTRs) are observed during steady-state infusion and/or during dosage reduction/cessation. With deep blockade, muscle activity may be present only during dosage reduction/cessation.
- Perform and document scheduled (i.e., every 4–8 h) ToF testing for patients receiving vecuronium and/or undergoing deep neuromuscular blockade (i.e., apnea or complete paralysis), and adjust dosage to achieve one-fourth (or more) twitch. If clinical goals cannot be met when one-fourth (or more) twitch is present during steady-state infusion, demonstrate one-fourth (or more) twitch during dosage reduction or cessation. Consider ToF testing in all patients.

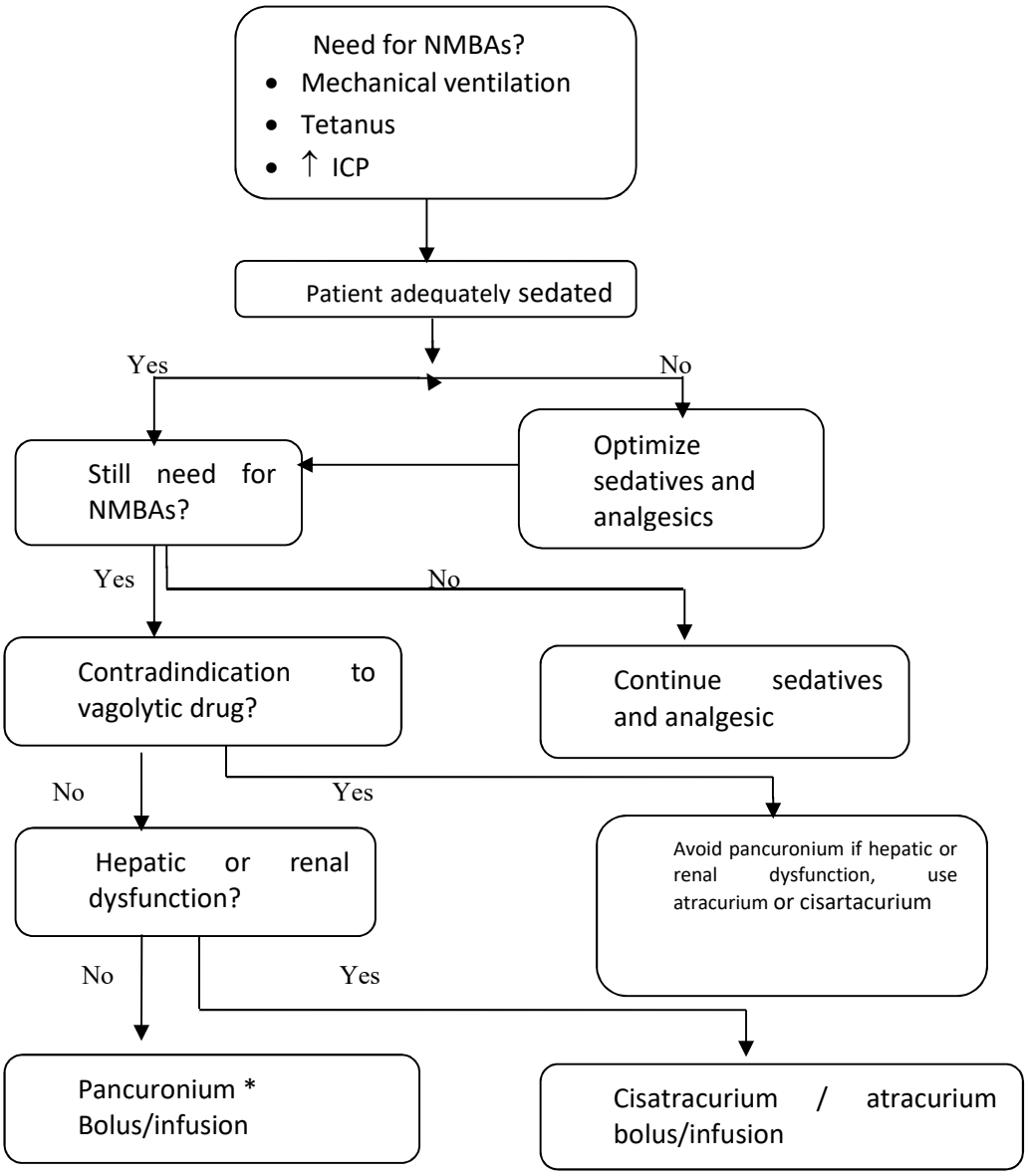

Figure 15: Use of neuromuscular blocking agents (NMBAs) in the intensive care unit. Monitor train-of-4 ratio, protect the patient's eyes, position the patient to protect pressure points, and address deep venous thrombosis prophylaxis. Reassess every 12 to 24 hours for continued NMBA indication. ICP, intracranial pressure[61]

Mechanical ventilation for the ARDS (acute respiratory distress syndrome).

Recent randomised clinical trials suggested that the use of cisatracurium is associated with better outcome in acute respiratory distress syndrome (ARDS). Its use has been associated with better outcomes in therapeutic hypothermia and in traumatic brain injury.[63]

Literature reports-8

Clinical outcomes were evaluated after 2 days of therapy with neuromuscular blocking agents in patients with early, severe ARDS in a multicenter, double-blind trial (funded by the French Ministry of Health) involving 340 patients presenting to the intensive care unit (ICU) with an onset of severe ARDS within the previous 48 hours. They were randomly assigned to receive, for 48 hours, either cisatracurium (n=178 patients) or placebo (162 patients). Severe ARDS was predefined. The hazard ratio for death at 90 days in the cisatracurium group, as

compared with the placebo group, was 0.68 (95% confidence interval [CI], 0.48 to 0.98; P = 0.04; which means a reduction of 32%), after adjustment. Mortality at 28 days was 23.7% (95% CI, 18.1 to 30.5) with cisatracurium and 33.3% (95% CI, 26.5 to 40.9) with placebo (P = 0.05). The rate of ICU-acquired paresis did not differ significantly between the two groups. The study concluded that **treatment with the neuromuscular blocking agent cisatracurium for 48 hours, early in the course of severe ARDS, improved the adjusted 90-day survival rate, increased the numbers of ventilator free days and days outside the ICU, and decreased the incidence of barotrauma during the first 90 days.** The mechanisms underlying the beneficial effect of neuromuscular blocking agents remain speculative.[64]

Patients treated with cisatracurium had fewer ventilator days (-1.01 d; P = 0.005) and ICU days (-0.98 d; P = 0.028) but were equally likely to be discharged home (odds ratio, 1.19; P = 0.056). When compared with vecuronium, cisatracurium was not associated with a difference in mortality but was associated with improvements in other clinically important outcomes. These data suggest that cisatracurium may be the preferred neuromuscular blocking agent for patients at risk for and with ARDS.[65]
Neuromuscular blocking agents (NMBAs) have been shown to improve the outcome of the most severely hypoxemic, acute respiratory distress syndrome (ARDS) patients. Being an expensive drug it is desirable to minimize its use without sacrificing on the patient management. A nurse-driven protocol based on TOF monitoring for NMBA administration in ARDS patients was able to decrease cisatracurium consumption without significantly affecting the quality of the neuromuscular block.[66]

It is to be noted that data on clinical and TOF monitoring of neuromuscular blockade are widely divergent in ICU patients receiving recommended doses of benzylisoquinoliniums (applies to both atracurium and cisatracurium).[67]

In subjects with early severe ARDS, the utilization of atracurium versus cisatracurium within 72 h of admission was not associated with significant differences in clinical outcomes.[68]

In the ICU cases the incidence of hypotension with continuous infusion was similar between atracurium and cisatracurium.[69]

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