Original Article

ISSN (0): 2456-7388; ISSN (P): 2617-5479

Efficacy of 4×ED_{95} Loading Dose of Cisatracurium Besylate for Endotracheal Intubation – A Clinical Study

Surbhi[1], S Nanda[2]

[1]Postgraduate student, Department of Anaesthesiology, M.K.C.G. Medical College and Hospital, Berhampur, Odisha, [2]Associate Professor, Department of Anaesthesiology, M.K.C.G. Medical College and Hospital, Berhampur, Odisha.

Abstract

Background: Cisatracurium besylate is the latest addition in the list of non-depolarizing neuromuscular blocking drugs. It has some very agreeable properties in terms of high potency with intermediate duration of action; but almost negligible production of Laudanosine, no histamine release and a major non-hepatic non-renal elimination. Various studies undertaken comparing different doses of Cisatracurium show that the dose for adequate intubating conditions lies between 0.15mg/kg to 0.2mg/kg. Since 0.2mg/kg (4×ED95) has been reported to have more haemodynamic stability, we decided to study its effects in terms of onset, intubating conditions, duration of action, reversibility and histamine release. **Subjects and Methods:** This study was conducted on 30 randomly selected patients of either sex between the ages of 18-60 years, undergoing elective surgical procedures under general anaesthesia with endotracheal intubation. All the patients were anaesthetized following standard and identical anaesthetic technique. Endotracheal intubation was facilitated with 0.2mg/kg of Inj.Cisatracurium. The quality of muscle relaxation was assessed purely on clinical observations. **Results:** With 4×ED95 dose we achieved excellent to good laryngoscopic view in almost all of our subjects within 3 minutes. All the patients had either excellent or good intubating conditions. Cisatracurium produced intermediate duration of action. The muscle relaxation produced by Cisatracurium was easily reversed with Neostigmine. There was no clinical evidence of histamine release. **Conclusion:** Cisatracurium in 2mg/kg (4×ED95) loading dose is an effective neuromuscular blocking agent devoid of histamine release.

Keywords: Cisatracurium, Neuromuscular blockade, 4xED_{95}.

Corresponding Author: Dr. S Nanda, Associate Professor, Department of Anaesthesiology, M.K.C.G. Medical College and Hospital, Berhampur, Odisha.

Received: April 2019
Accepted: May 2019

Introduction

Cisatracurium was first synthesized in 1989.[1] After further clinical development it was approved by the US Food and Drug Administration for human use in 1995. First marketed in UK under the trade name "Nimbex" in the year 1996, it has been recently introduced for clinical use in India in 2016. Formerly known as 51W89,[2] Cisatracurium (1R cis-1R'cis) is one of the 10 isomers of Atracurium. Although it is 15% of Atracurium by weight, yet it brings more than 50% of its neuromuscular blocking activity.[3] Major part (77%) of Cisatracurium undergoes Hofmann elimination and for the remaining 23%, clearance is organ dependant especially through kidneys(16%).[4] It is approximately four to five times as potent as Atracurium, and in contrast does not release histamine.[1,5] Also in comparison to Atracurium, the production of Laudanosine is five times less with Cisatracurium.[3]

Going through available literature, we observed that different studies have been done at different times using different doses to check its effectiveness to facilitate endotracheal intubation and maintain intraoperative muscle paralysis. The dose of any drug determines the time for onset of its action. Generally large doses result in quicker onset. The Effective Dose to produce pharmacological effect of a drug in 95% of population, termed as it's ED95 dose, is the amount of muscle relaxant needed to cause 95% depression of twitch height of adductor pollicis muscle. Usually 2-3 times ED95 dose is needed to obtain adequate relaxation of laryngeal muscles to enable endotracheal intubation.[6,7]

In 1996, Bluestein et al had reported that 2xED95 dose of Cisatracurium produces good or excellent intubating conditions in approximately 2 minutes. Whereas, the same conditions were obtained in 1.5 minutes when the intubating dose was either 3xED95 or 4xED95.[8] Studies conducted by Mandal et al and Schmautz et al showed that good to excellent intubating conditions can be obtained in about 90 seconds when Cisatracurium is administered in 4xED95 dose.[9,10] Other studies have shown that the loading dose of Cisatracurium required to achieve adequate intubating conditions is between 0.15mg/kg(3xED95) to 0.2mg/kg (4×ED95).[11,12] The time to achieve maximum blockade is between 2.7-5.2 minutes and clinical duration of response is 45-68 minutes.[4,13-17]

In view of the above differing opinions, we attempted to

examine the efficacy of this drug newly available to us to obtain intraoperative muscle relaxation, focussing particularly in its ability to produce adequate muscle paralysis to facilitate endotracheal intubation. Since most of the previous studies have reported that bolus dose of 4xED95, i.e., 0.2mg/kg provides the best conditions for endotracheal intubation in a shorter time, hence we decided to use that dose for our study.

AIM:

To study the neuromuscular blocking effects of 4×ED95 (0.2mg/kg) loading dose of Cisatracurium in terms of onset time, laryngoscopic view, intubating conditions, duration of action and reversibility.

Subjects and Methods

After obtaining the Institutional Ethical Committee clearance, this study was conducted in the Department of Anaesthesiology, M.K.C.G. Medical College and Hospital, Berhampur (Odisha) on randomly selected 30 adult patients of either sex posted for elective surgery under General Anaesthesia requiring endotracheal intubation.

Patients between 18 to 60 years of age of ASA Grades I and II3 with Modified Mallampati Class I and II3 were considered for study. Patients posted for emergency surgical procedures, pregnant or lactating females, patients giving history of hypersensitivity, malignant hyperthermia or any other neuromuscular disorder, and patients who during preoperative assessment were thought to pose difficulty in intubation were excluded from the study. All the participants were explained the purpose of the study. Subjects were enrolled only when they gave their written consent.

The patients were prescribed oral Tab.Ranitidine Hydrochloride(150mg) and Tab.Alprazolam(0.5mg) the night before surgery. On the day of surgery, in the operating room, baseline Heart rate, Non-invasive Blood pressure, Peripheral oxygen saturation(SpO2), five lead ECG, ETCO2, Surface temperature were recorded. All patients were premedicated with 10µg/kg of Inj.Glycopyrrolate, Inj.Midazolam(0.05mg/kg) and Inj.Fentanyl(1µg/kg) intravenously. Preoxygenation was done with 10 litres/min of 100% Oxygen for 3 minutes using Bain's coaxial circuit. Anaesthesia was induced with intravenous Inj.Propofol(2mg/kg) and Inj.Cisatracurium(0.2mg/kg) was given IV to facilitate tracheal intubation. Clinical criteria of muscle relaxation were observed for the analysis of the effects of Cisatracurium.

The onset of muscle relaxation was determined when there was decrease in amplitude of excursion of reservoir bag in the spontaneously breathing patient and they were manually ventilated for 3 minutes and then checked for relaxation of jaws. If jaw relaxation was found to be inadequate, then patients were ventilated for another 1 minute and rechecked. This process was followed till satisfactory relaxation of jaws was obtained. All patient's first assessment of jaw relaxation was done only after 3 minutes of completion of Cisatracurium administration. Time for adequate jaw relaxation was noted as from the time of completion of administration of Cisatracurium to complete jaw relaxation.

Laryngoscopy was performed with appropriate size MacIntosh blade and the position and movement of the vocal cords, presence of coughing and movement of diaphragm were checked. The quality of relaxation was assessed as per grading described by Schwarz et al in 1985.[18]

Schwarz's Grades of Relaxation

Excellent (Grade III)
- Jaw relaxed
- Vocal cords apart
- Vocal cords immobile
- No diaphragmatic movement

GOOD (Grade II)
- Jaw relaxed
- Vocal cords apart
- Vocal cords immobile
- Some diaphragmatic movement

POOR (Grade I)
- Jaw relaxed
- Vocal cords moving
- Coughing

INADEQUATE (Grade 0)
- Jaw poorly relaxed
- Vocal cords adducted
- Coughing

Patients were then intubated with appropriate size cuffed oral endotracheal tube and the ease of intubation was graded as per guidelines laid by Mehta et al (1985).[19]

Mehta's Gradation of Ease of Intubation:

Excellent (Grade I)
- Easy passage of tube without bucking

GOOD (Grade II)
- Passage of tube with slight bucking

FAIR (Grade III)
- Passage of tube with moderate bucking

IMPOSSIBLE (Grade IV)
- Intubation could not be performed with three attempts

Copenhagen Consensus Conference (CCC) Score (1995),[20] was also applied on all patients to check if Cisatracurium produced clinically acceptable muscle relaxation for endotracheal intubation.

Copenhagen Consensus Conference Score:

1. LARYNGOSCOPY Easy Fair Difficult
2. VOCAL CORDS
   - Position Abducted Intermediate Closed
   - Movement None Moving Closing
3. REACTION TO INTUBATION
   - Limbs None Slight Vigorous
   - Coughing None Diaphragm >10 sec

4. Scores Excellent Good Poor

Excellent: All scores excellent ----------CLINICALLY ACCEPTABLE
GOOD: All scores excellent or good----------CLINICALLY ACCEPTABLE
POOR: Any score poor----------CLINICALLY UNACCEPTABLE

After intubation, cuff of the tube was inflated. Successful endotracheal intubation was confirmed by chest wall movement, auscultation of bilaterally equal breath sounds and identification of CO2 in exhaled gas and the tube was fixed. Anaesthesia was maintained with Isoflurane (1%) and mixture of Nitrous oxide and Oxygen(60:40). Patients were manually ventilated. Further incremental doses of 0.03mg/kg of Inj. Cisatracurium were given IV when following feature(s) indicating insufficient relaxation were noted:

1. Tightness of rebreathing bag
2. Movement of limbs
3. Flickering respiratory movements
4. Inadequate surgical relaxation.

Time period between end of the administration of the loading dose and the first incremental dose was noted and was taken as the duration of action of Cisatracurium. Hemodynamic parameters like Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP), SpO2, ETCO2 and temperature were monitored throughout the duration of surgery. At the end of surgery neuromuscular blockade was reversed with Inj. Neostigmine (50µg/kg) combined with Inj. Glycopyrrolate (10µg/kg) and the endotracheal tube was removed after obtaining clinical signs of adequate reversal. The pharmacological quality of reversal of neuromuscular blockade was determined according to the following criteria given by Nunn in 1989:[21]

i) Sticking out tongue
ii) Wide opening of eyes
iii) Keeping head lifted for 5 seconds
iv) Ability to take deep breaths
v) Obeying verbal commands
vi) Moving and raising legs.

If the reversal was inadequate after 5minutes, repeat doses of Inj. Neostigmine were given and the total amount of Neostigmine required to reverse neuromuscular blockade was considered to determine the pharmacological quality of reversal. Adequacy of reversal was evaluated using the following 3-point rating scale:-

Good: Patient fully reversed with the initial Neostigmine dose.
Fair: More than initial dose of Neostigmine was required.
Poor: Patient did not breath despite additional doses of Neostigmine.

Any perioperative signs of histamine release (redness, erythema, wheal accompanied by hemodynamic changes or bronchospasm) were noted.

Results

Total 30 patients were studied. The demographic profile and other parameters are as shown in [Table 1].

Table 1: Demographic profile and other parameters.

Study Parameters	N=30
Age (yrs)	36.4±12.4
Sex (M:F)	13:17
Weight (Kg)	58.5±10.3
ASA (I:II)	24:6

(Values are expressed in Mean± Standard Deviation and Ratios)

Out of the 30 patients studied, in 29 cases adequate jaw relaxation was achieved within 3 minutes while only a single patient needed to be ventilated for another 1 minute [Table 2].

Table 2: Time for Adequate Jaw Relaxation

Jaw Relaxation Time (Min)	Patients (n=30)	
	Number	Percentage (%)
3	29	96.66
4	1	3.33
5	0	0

In the laryngoscopic view grading done as per criteria set by Schwarz et al, we obtained Grade III view in 83.33% patients in our study. While the view was Grade II in 10% cases and Grade I in only 6.66% patients [Table 3].

Table 3: Laryngoscopic Grading (Schwarz et al)

Grades	Patients (N=30)	
	Number	Percentage (%)
III	25	83.33
II	3	10
I	2	6.66
0	0	0

On assessment of ease of intubation as per guidelines set by Mehta et al, in our study 25 out of 30 patients(83.3%) had excellent (Grade I) intubating conditions. The intubating conditions were good (Grade II) in the remaining 5 patients (16.6%) with none scoring Grades III or IV [Table 4].

Table 4: Intubation Grading (Mehta et al)

Grades	Patients (N=30)	
	Number	Percentage (%)
I	25	83.33
II	5	16.66
III	0	0
IV	0	0

We obtained Excellent CCC score in 25(83.3%) patients out of total 30 and the score was Good in rest 16.6% with none scoring Poor(0) at all. [Table 5]

Table 5: Copenhagen Consensus Conference score (CCC)

CCC	Patients (n=30)	
	Number	Percentage (%)
EXCELLENT	25	83.33
GOOD	5	16.66
POOR	0	0

The mean duration of action with Inj. Cisatracurium was found to be 41.06±12.05 minutes in our study [Table 6].

Table 6: Duration of action

Mean Duration Of Action (min)	41.06±12.05

Out of the 30 patients administered Cisatracurium, 30% cases had a good reversal of neuromuscular blockade following the initial bolus dose of Neostigmine. But 21 patients (70%) needed one extra dose of Neostigmine to meet Nunn's criteria. However, no more doses were needed, nor did we note any failure of reversal in our study.

Table 7: Adequacy of Reversal

3 Point Rating Scale	Patients (N=30)	
	Number	Percentage (%)
Good	9	30
Fair	21	70
Poor	0	0

There were no clinical signs of histamine release in any of our cases. Only 1 patient had post-extubation laryngospasm which was managed with intravenous Propofol and oxygen support.

Discussion

We studied randomly selected 30 patients between ages 18-60 years (mean=36.4±12.4). The male:female ratio was 13:17 which was nearly symmetrical. Weight was measured solely for the purpose of dose calculation. Since our study involved effect of Cisatracurium in terms of its actions on the airway and duration of this effect, we didn't want our results to be influenced by other causes of difficult airway and any systemic diseases. Hence we included ASA Grades I and II patients with Mallampati class I and II airways only.

Available literature recommends Cisatracurium dose of 0.15mg/kg(3×ED95) to 0.2mg/kg(4×ED95) for endotracheal intubation.[4,13-17] We selected 0.2mg/kg because doses lower than that were associated with haemodynamic instability22 and we were not assessing the haemodynamic effects of Cisatracurium in our present study. Besides, we were observing whether the onset of action of Cisatracurium is beyond 3 minutes, which is the standard for most intermediate acting non-depolarizing muscle relaxants. Onset of action of Cisatracurium 0.15mg/kg as intubating dose is reported by some authors to be beyond 3 minutes.8 Doses higher than 4×ED95 have been used for rapid sequence intubation and reported to cause prolonged duration of action.[23] So we excluded those doses and used 0.2mg/kg dosage.

Properties of muscle relaxant of interest are its onset of effect, duration of action, the kind of laryngoscopic and intubating conditions it produces and how easily it's effects can it be reversed. We assessed all patients in terms of onset of action for satisfactory jaw relaxation, laryngoscopic view, ease of intubation, duration of action of Cisatracurium bolus dose of 0.2mg/kg and reversibility of muscle paralysis.

This study was based purely on observations of clinical parameters. We took jaw relaxation time as the measure of onset of action of Cisatracurium for endotracheal intubation. This was measured from completion of injection of the bolus dose of Cisatracurium to complete relaxation of jaw. We observed that in all of our patients except one (96.66%), jaw was acceptably relaxed within 3 minutes.

For clinical grading of intubating conditions, the laryngoscopic view helps to assess the usefulness of relaxant drugs for intubation purposes. According to criteria described by Schwarz et al, we obtained excellent view in 25 patients (83.33%). Whereas 3 and 2 number of our patients had good (10%) and fair(6.6%) views respectively.

We analysed intubation criteria as laid down by Mehta et al. In 25 patients(83.33%) we could intubate easily without observing any bucking. In 5 patients(16.66%) slight bucking was experienced although intubation was easy.

In our study 25 number of patients(83.33%) had excellent CCC score and 5 patients(16.66%) had good CCC score. Thus, providing 100% clinically acceptable muscle relaxation.

The mean duration of action of 4×ED95(0.2mg/kg) loading dose of Cisatracurium was found to be 41.06±12.05 minutes in our study.

Bluestein LS et al,[8] obtained good or excellent intubating conditions in over 90% of patients who received Cisatracurium 0.1mg/kg as compared to our study where 99.99% of patients receiving Cisatracurium 0.2mg/ kg had excellent to good intubating conditions. The higher percentage in our study may be due to the higher dosage used by us.

Study of pharmacodynamic dose-response and safety of Cisatracurium by Lepage JY et al,[24] in 1996 of doses between 0.025-0.25mg/kg revealed that Cisatracurium is a potent neuromuscular blocking drug with an intermediate duration of action but no apparent histamine release. We also made the same observation in our study. We obtained excellent to good intubating conditions in 99.99% of the cases. Effects lasted for 41.06±12.05 minutes on an average which points towards intermediate duration of action. And no patient in our study exhibited any clinical sign of histamine release.

M. T. Carroll et al,[25] in August 1998 had reported that Cisatracurium 0.1mg/kg and Cisatracurium 0.1mg/kg and 0.15mg/kg produced clinically acceptable intubating conditions in 73% and 87% patients respectively. Our study showed that Cisatracurium 0.2mg/kg had higher incidence of clinically acceptable conditions (99.9%). This difference is due to difference in dosage in our study. They noted that median duration of clinical muscle relaxation with Cisatracurium 0.15mg/kg was 51–59 minutes and Cisatracurium 0.1mg/kg was 45-48 minutes. With the dose of 0.2mg/kg, we observed the mean duration of action to be 41.06±12.05 minutes.

Mandal et al (2002) had observed that Cisatracurium 0.20mg/kg is the minimum dose required to obtain excellent to good intubating conditions.[9] We used the same dose. And upon applying Copenhagen Consensus Conference score, got excellent to good incubating conditions in 99.9% (100%) patients.

Conclusion

Thus we conclude from our study that Cisatracurium 0.2mg/kg (4xED95) single bolus dose is an efficient drug for performing endotracheal intubation without major side effects.

Limitations

Limitations of our study were:

1. Small sample size
2. Unavailability of neuromuscular monitor
3. Assessing jaw relaxation only after 3 minutes
4. Studying only single dose (0.2mg/kg) of the drug.

References

1. Wastila WB, Maehr RB, Turner GL, Hill DA, Phil. M, Savarese JJ. Comparative Pharmacology of Cisatracurium (51W89), Atracurium, and Five Isomers in Cats: Anesthesiology. 1996 Jul;85(1):169–77.
2. Meretoja OA, Taivainen T, Wirtavuori K. Pharmacodynamic effects of 51W89, an isomer of atracurium, in children during halothane anaesthesia. British journal of anaesthesia. 1995 Jan 31;74(1):6-11.
3. Miller RD, editor. Miller's anesthesia. Eighth edition. Philadelphia, PA: Elsevier/Saunders; 2015. 859-956 p.
4. Kisor DF, Schmith VD, Wargin WA, Lien CA, Ornstein E, Cook DR. Importance of the organ-independent elimination of cisatracurium. Anesthesia & Analgesia. 1996 Nov 1;83(5):1065-71.
5. Lien CA, Belmont MR, Abalos A, Eppich L, Quessy S, Abou-Donia MM, et al. The Cardiovascular Effects and Histamine-releasing Properties of 51W89 in Patients Receiving Nitrous Oxide/Opioid/Barbiturate Anesthesia: Anesthesiology. 1995 May;82(5):1131–8.
6. Miller RD. Miller's Anesthesia. 7th ed. Churchill Livingstone; 2009. CHAPTER 29.
7. Kopman AF, Klewicka MM, Neuman GG. Reexamined: the recommended endotracheal intubating dose for nondepolarizing neuromuscular blockers of rapid onset. Anesthesia & Analgesia. 2001 Oct 1;93(4):954-9.
8. Bluestein LS, Stinson LW, Lennon RL, Quessy SN, Wilson RM. Evaluation of cisatracurium, a new neuromuscular blocking agent, for tracheal intubation. Can J Anaesth. 1996 Sep;43(9):925–31.
9. Mandal P. Intubating Conditions after Cisatracurium Administration-A Dose Response Study in Adults. J Anaesth Clin Pharmacol. 2002;18:147–51.
10. Schmautz E, Deriaz H, Vrillon M, Lienhart A. Evaluation of 51W89 for endotracheal intubation in surgical patients during N2O/O2 propofol anesthesia. InAnesthesiology 1994 Sep 1 (Vol. 81, No. 3 A, pp. A1081-A1081).
11. Kirov K, Motamed C, Decailliot F, Behforouz N, Duvaldestin P. Comparison of the neuromuscular blocking effects of cisatracurium and atracurium on the larynx and the adductor pollicis. Acta Anaesthesiologica Scandinavica. 2004 May;48(5):577-81
12. Correa CM, Sudo GZ, Sudo RT. Hemodynamic effects of atracurium and cisatracurium and the use of diphenhydramine and cimetidine. Revista brasileira de anestesiologia. 2010 Feb;60(1):52-63.
13. Belmont MR, Lien CA, Quessy S, Abou-Donia MM, Abalos A, Eppich L, Savarese JJ. The clinical neuromuscular pharmacology of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anesthesia. Anesthesiology: The Journal of the American Society of Anesthesiologists. 1995 May 1;82(5):1139-45.
14. Savarese JJ, Lien CA, Belmont MR, Wastila WB. The clinical pharmacology of new benzylisoquinoline-diester compounds, with special consideration of cisatracurium and mivacurium. Der Anaesthesist. 1997 Oct;46(10):840-9.
15. Naguib M, Samarkandi AH, Ammar A, Elfaqih SR, Al-Zahrani S, Turkistani A. Comparative clinical pharmacology of rocuronium, cisatracurium, and their combination. Anesthesiology: The Journal of the American Society of Anesthesiologists. 1998 Nov 1;89(5):1116-24.
16. Kim KS, Chung CW, Shin WJ. Cisatracurium neuromuscular block at the adductor pollicis and the laryngeal adductor muscles in humans. British journal of anaesthesia. 1999 Sep 1;83(3):483-4.
17. Boyd AH, Eastwood NB, Parker CJ, Hunter JM. Pharmacodynamics of the 1R cis-1'R cis isomer of atracurium (51W89) in health and chronic renal failure. BJA: British Journal of Anaesthesia. 1995 Apr 1;74(4):400-4.
18. Schwarz S, Ilias W, Lackner F, Mayrhofer O, Foldes FF. Rapid tracheal intubation with vecuronium: the priming principle. Anesthesiology. 1985 Apr;62(4):388-91.
19. Mehta MP, Choi WW, Gergis SD, Sokoll MD, Adolphson AJ. Facilitation of rapid endotracheal intubations with divided doses of nondepolarizing neuromuscular blocking drugs. Anesthesiology. 1985 Apr;62(4):392-5.
20. Viby□Mogensen J et al. Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents. Acta Anaesthesiologica Scandinavica. 1996 Jan;40(1):59-74.
21. Nunn JF, Utting JE, Brown BR. General Anesthesia. 1989.5:151-157, 169-174
22. El-Kasaby AM, Atef HM, Helmy AM, El-Nasr MA. Cisatracurium in different doses versus atracurium during general anesthesia for abdominal surgery. Saudi J Anaesth. 2010 Sep;4(3):152–7.
23. Teymourian H, Samet MA, Mohajerani SA, Jafari A. Comparison of modified and high dose of cisatracurium for rapid-sequence intubation. Asian J Pharm Nurs Med Sci. 2014;2:110-5.
24. Lepage JY, Malinovsky JM, Malinge M, Lechevalier T, Dupuch C, Cozian A, et al. Pharmacodynamic dose-response and safety study of cisatracurium (51W89) in adult surgical patients during N2O-O2-opioid anesthesia. Anesth Analg. 1996 Oct;83(4):823–9.
25. Carroll MT, Mirakhur RK, Lowry D, Glover P, Kerr CJ. A comparison of the neuromuscular blocking effects and reversibility of cisatracurium and atracurium. Anaesthesia. 1998 Aug;53(8):744–8.

How to cite this article: Surbhi, Nanda S. Efficacy of 4×ED95 Loading Dose of Cisatracurium Besylate for Endotracheal Intubation – A Clinical Study. Acad. Anesthesiol. Int. 2019;4(1):104-108.

DOI: dx.doi.org/10.21276/aan.2019.4.1.24

Source of Support: Nil, **Conflict of Interest:** None declared.