Cisatracurium Besilate
A Review of its Pharmacology and Clinical Potential in Anaesthetic Practice

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Cisatracurium besilate (besylate) is a nondepolarising neuromuscular blocking agent with an intermediate duration of action. It is the R-cis,R'-cis isomer of atracurium besilate and is approximately 3-fold more potent than the mixture of isomers that constitute the parent drug. The ED95 for cisatracurium besilate (dose required to produce 95% suppression of twitch response to nerve stimulation) in adults is 0.05 mg/kg during N2O/O2 opioid anaesthesia.

As for atracurium besilate, the primary route of elimination of cisatracurium besilate is by spontaneous degradation. Cisatracurium besilate is not associated with dose-related histamine release (at bolus doses of ≤8 × ED95) and, consistent with this, has demonstrated cardiovascular stability in both healthy patients (≤8 × ED95) and those with coronary artery disease (≤6 × ED95).

In clinical trials, cisatracurium besilate has been used successfully to facilitate intubation (at 2 to 4 × ED95) and as a muscle relaxant during surgery and in intensive care. Compared with vecuronium, cisatracurium besilate was associated with a significantly faster recovery after continuous infusion in patients in intensive care.

Relative to atracurium besilate, cisatracurium besilate has a lower propensity to cause histamine release, is more potent but has a slightly longer onset time at equipotent doses. It also offers a more predictable recovery profile than vecuronium after prolonged use in patients in intensive care. Thus, comparative data provide some indication of the potential of cisatracurium besilate as an intermediate-duration neuromuscular blocking agent but further comparisons with other like agents are required to define precisely its relative merits.

The ED95 of cisatracurium besilate (dose required to produce 95% suppression of twitch response to nerve stimulation) is approximately 0.05 mg/kg in adults and children during N2O/O2/opioid anaesthesia and 0.04 mg/kg during halothane/N2O/O2 anaesthesia in children.

The degree and duration of neuromuscular block produced by cisatracurium besilate increases and time to maximum neuromuscular block decreases in a dose-dependent manner. Cisatracurium besilate 0.1 mg/kg (2 × ED95) produces 99 to 100% twitch suppression within 4.6 to 5.8 minutes compared with 2.4 to 3.7 minutes after a 0.15 mg/kg dose (3 × ED95) and 2.7 to 3.8 minutes after 0.2 mg/kg (4 × ED95). The time to maximum effect was 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.

Clinical duration of neuromuscular block (i.e. time from injection to 25% twitch recovery) ranges from 33 to 45 minutes after cisatracurium besilate 0.1 mg/kg (2 × ED95) and is approximately 55 minutes after cisatracurium besilate 0.15 mg/kg (3 × ED95) during either barbiturate/N2O/O2 or propofol/N2O/O2 anaesthesia. Doubling the dose of cisatracurium besilate from 0.1 to 0.2 mg/kg increased the clinical duration of effect by 16 to 23 minutes. Once started, recovery (i.e. 5 to 95% or 25 to 75% recovery indices) was independent of dose over the range 0.1 to 0.4 mg/kg.

Recovery rate was unaffected by age, renal failure or end-stage liver disease, but appeared to be slower following the use of sevoflurane in children. As for other nondepolarising agents, recovery from neuromuscular block with cisatracurium besilate can be effectively accelerated by administration of an anticholinesterase agent once recovery has started.
Cisatracurium besilate, at doses of ≤8 × ED₉₅ in adult patients, was not associated with any significant changes in mean blood pressure or heart rate. In patients with coronary artery disease, doses of ≤6 × ED₉₅ were not associated with a ≥20% decrease in mean arterial pressure in any patient; the incidence of other haemodynamic changes did not differ between cisatracurium besilate (0.1 or 0.3 mg/kg) or vecuronium (0.1 or 0.3 mg/kg) recipients. Cisatracurium besilate at doses of ≤8 × ED₉₅ is not associated with dose-related changes in median plasma histamine levels.

Cisatracurium besilate undergoes temperature and pH-dependent chemical (Hofmann) degradation. This is the main route by which the drug is broken down and accounts for 77% of its total clearance. Cisatracurium besilate degrades to form laudanosine and the corresponding monoquaternary acrylate (which in turn is broken down to a monoquaternary alcohol and then laudanosine). Although the liver and kidneys play only a small role in the excretion of cisatracurium besilate, urinary and hepatic elimination pathways are important for the metabolites of laudanosine.

The apparent volume of distribution of cisatracurium besilate at steady-state ranges from 0.11 to 0.16 L/kg in healthy adults. However, because these values do not allow for peripheral elimination of the drug, it is likely that they are underestimates. Cisatracurium besilate is cleared from the body at a rate of 0.27 to 0.34 μg/kg/h, with an elimination half-life of 22 to 35 minutes.

Good or excellent intubating conditions were achieved after 120 seconds in 89 to 100% of patients receiving cisatracurium besilate 0.15 mg/kg (3 × ED₉₅). This was a similar result to that achieved with atracurium besilate 0.5 mg/kg (2 × ED₉₅) after 120 seconds. At 4 × ED₉₅ of cisatracurium besilate (0.2 mg/kg), good or excellent intubating conditions were generally achieved after 90 seconds in 95 to 100% of patients; poorer results attained with this dose in 2 European studies may have been attributable to the fact that midazolam was not administered as part of the induction regimen.

In adult patients undergoing elective surgery, the mean infusion rate of cisatracurium besilate required to maintain approximately 95% block ranged from 1.2 to 1.5 μg/kg/min during N₂O/O₂/opioid or propofol anaesthesia. Mean infusion requirements for children (aged 2 to 12 years) were 1.6 and 1.8 μg/kg/min in 2 studies. The 25 to 75% recovery index ranged from 15 to 18 minutes in adults and 11 or 14 minutes in children after a continuous infusion of cisatracurium besilate. Limited data indicate that recovery is independent of duration of infusion or the number of maintenance doses administered, but this requires confirmation.

For adult patients in intensive care, the mean infusion rate of cisatracurium besilate required to maintain adequate neuromuscular block ranged between 2.6 and 3.2 μg/kg/min. The mean time to 70% recovery of the ratio of the fourth to the first train-of-four response after an infusion duration of at least 12 hours was significantly faster in cisatracurium besilate than vecuronium recipients (68 vs 387 minutes).

According to an overview of all clinical data (n = 946), events possibly related to cisatracurium besilate were bradycardia (0.4%), hypotension (0.2%), flushing (0.2%), bronchospasm (0.2%) and rash (0.1%). No event was reported at a frequency of >1%. In comparative clinical studies, flushing was reported in 0% of
patients receiving cisatracurium besilate (2 to 4 × ED95) versus 0 to 11% of patients receiving atracurium besilate (2 × ED95).

In adult patients, cisatracurium besilate 0.15 or 0.2 mg/kg following induction with propofol/N2O/O2 generally produces good or excellent intubating conditions at 2 and 1.5 minutes, respectively. A longer time to intubation may be required in the elderly, in patients with renal failure or with lower doses of cisatracurium besilate. In children (aged 2 to 12 years), the recommended initial dose is 0.1 mg/kg administered during halothane or opioid anaesthesia. Doses should be individualised and neuromuscular function should be monitored during drug administration, as for any muscle relaxant.

For prolonged surgery, maintenance doses of cisatracurium besilate 0.03 mg/kg should be used. Each additional maintenance dose maintains neuromuscular block for approximately 20 minutes. For continuous infusion of cisatracurium besilate, an initial infusion rate of 3 μg/kg/min is suggested, followed by a rate of 1 to 2 μg/kg/min to maintain 89 to 99% block during opioid/N2O/O2 anaesthesia. A 30 to 40% reduction in infusion rate should be considered during isoflurane or enflurane anaesthesia; greater reductions may be necessary if anaesthesia is prolonged.

In adult patients in intensive care, an infusion rate of approximately 3 (range 0.5 to 10.2) μg/kg/min should provide adequate neuromuscular block, although requirements may vary with time.

Cisatracurium besilate (besylate) is a non-depolarising neuromuscular blocking agent with an intermediate duration of action.[11] It is a benzylisoquinolinium compound (fig. 1) and is a purified form of 1 of the 10 stereoisomers that constitute atracurium besilate (R-cis,R’-cis isomer); it makes up about 15% of the atracurium besilate preparation.[2] Like atracurium besilate, cisatracurium besilate undergoes spontaneous (or Hofmann) degradation at physiological pH and temperature.

Throughout this review, doses of cisatracurium besilate will be expressed in terms of the bis-cation (molecular weight 929), in line with current convention, rather than as the besilate salt (molecular weight 1244). However, doses of atracurium besilate, in keeping with the references from which they are quoted, are expressed in terms of the besilate salt.

### 1. Pharmacodynamic Properties

#### 1.1 Neuromuscular Blocking Effects

The neuromuscular blocking activity of single bolus doses of cisatracurium besilate in various patient groups is presented in table I. Its effects after multiple bolus doses or a continuous infusion are reviewed in sections 3.2 and 3.3. In all studies, neuromuscular function was assessed by either mechano- or electromyography of contraction of the adductor pollicis muscle induced by a supra-maximal single pulse or train-of-four (TOF) stimulus to the ulnar nerve.

**1.1.1 Onset**

From dose-response data, the dose of cisatracurium besilate required to produce 95% suppression of twitch response (ED95) was estimated to be 0.05 mg/kg in adults during N2O/O2/opioid anaesthesia.[1,3] In children (aged 2 to 12 years), the estimated ED95 was 0.04 mg/kg during halothane/N2O/O2 anaesthesia[16] and approximately 0.05 mg/kg during N2O/O2/opioid anaesthesia.[13] Cisatracurium besilate is 3.2 to 3.5 times more potent than atracurium besilate (when the dose of atracurium besilate is expressed in terms of the cation) in humans.[1,3,14]

The degree and duration of neuromuscular
block produced by cisatracurium besilate increases and the time to onset of block decreases in a dose-dependent manner. In dose-finding studies, cisatracurium besilate 0.1 mg/kg (2 × ED95) produced 99 to 100% twitch suppression within 4.6 to 5.8 minutes during barbiturate or propofol/N2O/O2 anaesthesia. The time to maximum suppression was slightly greater than that achieved with 2 × ED95 (0.5 mg/kg) of atracurium besilate (2.3 to 4.0 minutes; table 1). Higher dosages of cisatracurium besilate produced maximum suppression within a progressively shorter time [2.4 to 3.7 minutes after 0.15 mg/kg (3 × ED95); 2.7 to 3.8 minutes after 0.2 mg/kg (4 × ED95); and 1.9 minutes after 0.4 mg/kg (8 × ED95)]. The time to 90% block (an indication of time to intubation) with cisatracurium besilate (2 × ED95) ranged from 2.2 to 2.5 minutes in adults and from 1.6 to 2.6 minutes in children.

Compared with that in healthy adults, the time to maximum neuromuscular block after cisatracurium besilate 0.1 mg/kg was delayed by approximately 1 minute in the elderly and patients with renal failure and shortened by almost 1 minute in patients with end-stage liver disease. However, the maximum block attained as well as the clinical duration were unaffected in any of these patient groups (table 1). In children, time to maximum neuromuscular block was 2.2 minutes after cisatracurium besilate 0.08 mg/kg and 2.3 to 2.8 minutes after a 0.1 mg/kg dose; another study (presented as an abstract) reported a greater value of 4.2 minutes but the reason for this was unclear.

The time to onset of neuromuscular block and the maximum block achieved with cisatracurium besilate did not appear to be affected by either the speed of injection (20 to 30 vs 5 to 10 seconds) or the induction agent used (propofol or thiopental sodium; table 1). The 4 studies which used isoflurane for the maintenance of anaesthesia did report shorter times to onset of block (3.0 to 4.2 vs 4.6 to 5.8 minutes with barbiturate or propofol/N2O/O2 anaesthesia; table 1); however, the fact that patients were anaesthetised with isoflurane for more than 15 minutes before administration of cisatracurium besilate in some of these studies is likely to have influenced these results (see section 5).

### 1.1.2 Recovery

**Spontaneous Recovery**

Clinical duration of neuromuscular block (i.e., time from injection to 25% twitch recovery) ranged from 33 to 45 minutes after a single bolus dose of cisatracurium besilate 0.1 mg/kg (2 × ED95) in dose-finding studies during either barbiturate or propofol/N2O/O2 anaesthesia. This was similar to the duration of neuromuscular block after an equipotent dose of atracurium besilate; although 1 study reported a 9-minute greater clinical duration with atracurium besilate, this was not statistically significant. Doubling the dose of cisatracurium besilate from 0.1 to 0.2 mg/kg increased the clinical duration...
Table I. Onset of and spontaneous recovery from neuromuscular block produced by single bolus doses of cisatracurium besilate (C) or atracurium besilate (A) in various patient groups undergoing elective surgery. Neuromuscular function was assessed by measuring the mechanomyogram or electromyogram of thumb adduction stimulated using either a supramaximal single pulse or train-of-four stimulus delivered to the ulnar nerve. Data are presented as mean values with the exception of 2 studies which reported median values.

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<th>Recovery (min)</th>
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a Not all measurements were made in all patients.
b Time to maximum neuromuscular block.
c Time from injection to 5, 25 (clinical duration) or 95% twitch (T1) recovery.
d Time taken for T1 to recover from 25 to 75% of baseline.
e Abstract.
f Historical control group. No more details of regimen provided for O'Neill & Foley.12

Abbreviations and symbols: E = enflurane; F = fentanyl; H = halothane; I = isoflurane; M = midazolam; P = propofol; S = sevoflurane; T = thiopental sodium; T1 = first train-of-four response or single twitch; p < 0.05 vs C 0.1 mg/kg; ** p < 0.05 vs C 0.1 and 0.15 mg/kg; * p < 0.01 vs adults; † † p < 0.001 vs sevoflurane anaesthesia.

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cal duration by 16 to 23 minutes. The clinical duration after a 0.15 mg/kg dose of cisatracurium besilate (3 x ED95) was 52 and 55 minutes in 2 studies.\[8,15\]

The mean 25 to 75% recovery index (or interval 25 to 75%) for cisatracurium besilate 0.1 mg/kg ranged from 8 to 13 minutes in adults\[1,3,15\] and was approximately 11 minutes in children.\[13\] Recovery from neuromuscular block was independent of cisatracurium dose over the range 0.1 to 0.4 mg/kg; neither the 5 to 95% nor the 25 to 75% recovery indices varied significantly with the dose administered.\[1\] This was supported by a report of an infant overdosed with cisatracurium besilate 0.86 mg/kg (\(\approx 22 \times \text{ED95}\)) in whom the 25 to 75% index was 10 to 15 minutes.\[17\]

Spontaneous recovery was generally unaffected by older age,\[1,5,6\] renal failure\[9\] or end-stage liver disease,\[11\] although there have been 2 reports of delayed recovery in elderly patients (clinical duration of 81 and 87 minutes).\[15\] Cisatracurium besilate appeared to have a slightly shorter clinical duration in children (27 to 34 minutes after 2 x ED95) than in adults,\[10,12,13\] although this was notably longer during sevoflurane anaesthesia (46 minutes).\[12\] Recovery from neuromuscular block with cisatracurium besilate was unaffected by prior administration of suxamethonium chloride,\[18\] an agent commonly used to aid tracheal intubation.

**Pharmacological Reversal**

As for other nondepolarising agents, recovery from neuromuscular block with cisatracurium besilate can be effectively accelerated by administration of an anticholinesterase agent once recovery is under way. The mean time to 95% twitch recovery was reduced to between 6 and 12 minutes if neostigmine was administered after 10 to 15% twitch recovery.\[3,15\] If neostigmine was administered after 16 to 30% recovery of muscle function, the time to 95% recovery was reduced further to 3 to 4 minutes.\[3,16\] The 25 to 75% index was consistently reduced to between 2 and 3 minutes after administration of neostigmine.\[1,3,16\]

### 1.2 Cardiovascular Effects

At doses of up to and including 8 x ED95 (generally administered over 5 to 10 seconds), cisatracurium besilate was not associated with any significant changes in mean blood pressure or heart rate in healthy adult patients anaesthetised with thiopental sodium/N₂O/O₂/fentanyl/midazolam.\[3,19\] Mean maximum changes in heart rate and mean arterial pressure ranged from a reduction of 3% to an increase of 3%.\[19\] Similarly, in children mean maximum increases of 1 to 4% were observed in mean arterial pressure and heart rate after cisatracurium besilate (2 x ED95) during either halothane/N₂O/O₂ or thiopental sodium/N₂O/O₂ anaesthesia.\[13,16\]

In patients with coronary artery disease (n = 115), cisatracurium besilate 0.1 or 0.3 mg/kg (i.e. \(\leq 6 \times \text{ED95}\)) was not associated with a \(\geq 20\%\) decrease in mean arterial pressure in any patient.\[20,21\] The incidence of haemodynamic changes (\(\geq 20\%\) changes in mean arterial pressure, heart rate, mean pulmonary arterial pressure, pulmonary capillary wedge pressure or cardiac output) did not differ between patients receiving cisatracurium besilate (0.1 or 0.3 mg/kg) and those receiving vecuronium (0.1 or 0.3 mg/kg).\[20,22\] However, when group mean values were considered, both drugs were associated with small but statistically significant decreases in heart rate,\[20,21\] cardiac output,\[20\] right atrial pressure,\[21\] mean pulmonary arterial pressure\[21\] and pulmonary capillary wedge pressure\[21\] versus baseline.

Benzylisoquinolinium compounds can produce mild to moderate haemodynamic changes secondary to inducing histamine release. Cisatracurium besilate at doses of \(\leq 8 \times \text{ED95}\) was not associated with any apparent dose-related changes in median plasma histamine levels, although there was great interpatient variation.\[3,19\] By comparison, a significant increase in median plasma histamine concentrations was observed 2 minutes after rapid administration of atracurium besilate in one study.\[3\] Two-fold or greater increases in histamine levels (to at least 1000 ng/L) were reported in 5 patients receiving doses of cisatracurium besilate ranging...
from 2 to 5 × ED₉₅[3,19] however, these changes were not accompanied by clinical signs of histamine release (e.g. cutaneous flushing, decreased blood pressure or increased heart rate) in any patient.[3,19]

1.3 Pharmacological Activity of Metabolites

To date, the pharmacological activity of the major breakdown products of cisatracurium besilate (laudanosine, the monoquaternary acrylate and alcohol and tetrahydropapaverine; section 2.2) has not been investigated. There are some data pertaining to the activity of the metabolites of atracurium besilate in animals, but whether or not these can be directly extrapolated to cisatracurium besilate is unknown. Although the breakdown products of atracurium and cisatracurium besilate are the same (section 2.2), the stereoisomeric make-up of these products and hence their pharmacological activity may differ. The greater potency of cisatracurium besilate versus atracurium besilate (section 1.1.1) also means that the concentrations of laudanosine achieved after administration of cisatracurium besilate (section 2.2) are lower than those observed after administration of atracurium besilate.

In anaesthetised cats, monoquaternary acrylate and monoquaternary alcohol had dose-dependent neuromuscular blocking activity over the dose range 0.1 to 4 mg/kg; laudanosine was devoid of neuromuscular blocking activity over the same dose range. No data were provided for atracurium besilate.[23]

Laudanosine can produce CNS excitatory effects in animals. In dogs, Chapple et al.[24] reported electroencephalogram abnormalities at plasma laudanosine concentrations >10 000 µg/L and epileptogenic activity at concentrations >17 000 µg/L. Volatile anaesthetics have been shown to increase the threshold for CNS effects of laudanosine in rabbits.[25] A relationship between plasma laudanosine concentrations and CNS effects in humans has not been established.

2. Pharmacokinetic Properties

The pharmacokinetic properties of cisatracurium besilate in healthy adults, the elderly, patients with renal failure or end-stage liver disease and those in intensive care are summarised in table II. Cisatracurium besilate was administered as a single intravenous infusion over 5 to 10 seconds[5,6,11,26-28] or as a continuous infusion.[29,30] The possible influence of concomitant anaesthetic or analgesic agents on the kinetics of cisatracurium besilate has not been systematically studied to date. For a detailed discussion of the population pharmacokinetics/pharmacodynamics of cisatracurium besilate, the reader is referred to an article by Schmith et al.[42]

2.1 Distribution

Estimates of the mean apparent volume of distribution of cisatracurium besilate at steady-state (Vₚₛ) in healthy adults ranged from 0.11 to 0.16 L/kg (table II). This was increased by 17 and 37% in elderly patients[5,6] and by 21% in patients with end-stage liver failure.[11] However, values for Vₚₛ obtained from these studies are likely to be underestimates, as the models used for data analysis assume that cisatracurium besilate is eliminated from the central compartment only. In fact, the drug undergoes Hofmann degradation (section 2.2) and so is cleared from both central and peripheral compartments. Using compartmental models (which considered elimination from both compartments), Vₚₛ was found to be underestimated by 17 to 20% compared with models that considered elimination from the central compartment only.[26,31]

2.2 Metabolism

Like atracurium besilate, cisatracurium besilate primarily undergoes pH- and temperature-dependent chemical (or Hofmann) degradation, although other routes are involved. Kisor et al.,[31] using data obtained from 31 healthy adults, estimated that the contribution of Hofmann degradation to the total clearance of cisatracurium besilate was 76.9%; or-
gan-dependent clearance accounted for the remaining 23.1%. Renal clearance was estimated to account for 16.4% of the total, and was therefore the main non-Hofmann route of elimination.[31] Hofmann degradation is highly dependent on pH; a 6-fold decrease in the in vitro half-life of cisatracurium besilate was observed as the pH increased from 6.4 to 7.8.[32]

Laudanosine and a corresponding monoquaternary acrylate are the products of Hofmann degradation of cisatracurium besilate (and atracurium besilate). The monoquaternary acrylate is thought to undergo hydrolysis by nonspecific plasma esterases to form the respective monoquaternary alcohols, which in turn also undergoes chemodegradation to form laudanosine (fig. 2).[32] There is evidence that laudanosine is then N-demethylated to yield tetrahydropapaverine.[33] All putative metabolites (laudanosine, the monoquaternary acrylate, alcohol and acid, and tetrahydropapaverine) and cisatracurium are found in the urine of humans, as well as O-glucuronic acid conjugates of monodemethyl laudanosine and monodemethyl tetrahydropapaverine.[33] It seems unlikely that cisatracurium besilate itself undergoes ester hydrolysis, as a corresponding monoquaternary acid metabolite was not detected in plasma samples after administration of the drug.[11,26]
Peak concentrations of laudanosine after administration of cisatracurium besilate 0.1 mg/kg in various patient groups ranged from 16 to 38 µg/L (table III). By comparison, mean peak laudanosine concentrations ranged from 149 to 345 µg/L after a single bolus dose of atracurium besilate 0.3 to 0.6 mg/kg in the same patient groups (table III). In patients with renal failure, plasma laudanosine concentrations were significantly higher than in healthy adults 30 to 240 minutes after administration of cisatracurium besilate; a similar increase was also evident in this patient group after administration of atracurium besilate. These data are consistent with renal clearance being the major route of elimination of laudanosine.

2.3 Elimination

The rate of clearance of cisatracurium besilate from the plasma in healthy adults ranged from 0.27 to 0.34 to L/h/kg (4.6 to 5.7 ml/min/kg; table II), but was reduced by 13% in patients with renal failure and increased by 16% in end-stage liver disease; these changes are unlikely to be clinically significant. Cisatracurium besilate was undetectable in the plasma 90 to 150 minutes after administration (limit of detection 10 µg/L). The elimination half-life ($t_{1/2}$) of cisatracurium besilate in healthy adults ranged from 22 to 35 minutes (table II). Compared with that in healthy adults, $t_{1/2}$ was 19 to 28% longer in the elderly (4- to 8-minute increase) and 14% longer in patients with renal failure (4-minute increase).

After administration of $[14C]$cisatracurium besilate to healthy volunteers, 95% of radioactivity was excreted in the urine and 4% in the faeces; <10% of the dose was recovered as unchanged par-

---

**Fig. 2.** Suggested degradation pathway of cisatracurium. A Hofmann degradation of the monoquaternary alcohol occurs at a slower rate than that of cisatracurium.
ent drug in the urine.\textsuperscript{42} Most of the radioactivity recovered was as demethyl metabolites of laudanosine,\textsuperscript{42} possibly corresponding with the conjugated monodemethyl metabolites identified by Dear et al.\textsuperscript{133} (section 2.2). The estimated mean $t_{1/2}\beta$ of laudanosine ranged from 3.6 to 5.4 hours.\textsuperscript{26,28} This was increased in 2 patients with end-stage liver disease (to 7.2 and 8.2 hours), consistent with the fact that laudanosine undergoes hepatic elimination.\textsuperscript{111}

### 3. Clinical Potential

Cisatracurium besilate has been investigated in 2 different clinical settings: in patients undergoing elective surgery (to facilitate tracheal intubation or to provide neuromuscular block during surgery) and in patients in intensive care.

#### 3.1 Tracheal Intubation

All trials investigating the use of cisatracurium besilate to facilitate tracheal intubation were randomised and recruited patients undergoing elective surgery of low to moderate risk (table IV). In most studies, the neuromuscular blocking agent was administered immediately after loss of consciousness (loss of eyelid reflex), although there was a 3- to 5-minute delay following induction to allow for baseline monitoring of muscle function in 2 studies.\textsuperscript{7,15} Intubation was attempted 60 to 120 seconds later. The investigator performing intubation was blinded to the neuromuscular blocking agent used, except in 2 studies in which some treatment groups were assessed in a nonblinded manner.\textsuperscript{7,15} Intubating conditions were graded subjectively according to a 4-point scale (although details of the scale were not provided for all studies\textsuperscript{7,45,47}). Propofol [with or without lidocaine (lignocaine)] or thiopental sodium and fentanyl were used as induction agents in all studies. In the US studies,\textsuperscript{15,45,47} midazolam and fentanyl were typically administered in advance of the induction agent.

Good or excellent conditions for intubation were observed in 89 to 100% of patients 120 seconds after cisatracurium besilate 0.15 mg/kg (3 x ED\textsubscript{95}),\textsuperscript{7,15,43-45} a similar result to that achieved 120 seconds after atracurium besilate 0.5 mg/kg (2 x ED\textsubscript{95}).\textsuperscript{15,43,45} In general, good or excellent results were achieved at 90 seconds in over 90% of patients after higher doses of cisatracurium besilate (4 or 6 x ED\textsubscript{95}), although 2 European studies\textsuperscript{7,43} reported poorer intubation results with the 0.2 mg/kg dose after 90 seconds (75 or 76% of patients). This may be attributable to midazolam not being administered as part of the induction regimen.\textsuperscript{144} A lower dose of cisatracurium besilate 0.1 mg/kg (2 x ED\textsubscript{95}) was associated with variable results at 120 seconds (67 to 89% of patients had good or excellent intubating conditions).\textsuperscript{7,15,43,45}
A comparative trial, presented as an abstract, reported similar intubating conditions 60 seconds after cisatracurium besilate 0.4 mg/kg (8 × ED95) or rocuronium 0.9 mg/kg (3 × ED95; table IV). The dose of cisatracurium besilate used in this trial is higher than that recommended for intubation (see section 5) and, as would be expected, was associated with a longer clinical duration than rocuronium. Another study, reported as an abstract, demonstrated that cisatracurium besilate 0.15, 0.2 and 0.3 mg/kg provided good or excellent intubating conditions in at least 90% of patients after 90 seconds when propofol or thiopental sodium was used as an induction agent (table IV).

Table IV. Intubating conditions after single bolus doses of cisatracurium besilate (C). Summary of randomised, intubator-blinded studies involving adult patients (American Society of Anesthesiologists grade I or II) undergoing elective surgery. Except where stated otherwise, neuromuscular blocking agents were administered immediately following loss of consciousness (loss of eyelid reflex)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Dose mg/kg</th>
<th>x ED95</th>
<th>No. of evaluable patients</th>
<th>Induction agent(s)</th>
<th>Time from dose to intubation (sec)</th>
<th>Intubating conditions (% patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose comparisons and comparisons with atracurium besilate (A)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bluestein et al.</td>
<td>C 0.1</td>
<td>2</td>
<td>18</td>
<td>M,P + L,F</td>
<td>120</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>C 0.15</td>
<td>2</td>
<td>18</td>
<td>M,P + L,F</td>
<td>120</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>C 0.2</td>
<td>4</td>
<td>19</td>
<td>M,P + L,F</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>Littlejohn et al.</td>
<td>C 0.1</td>
<td>2</td>
<td>18</td>
<td>P + L,F</td>
<td>120</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>C 0.15</td>
<td>3</td>
<td>19</td>
<td>P + L,F</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>C 0.2</td>
<td>4</td>
<td>21</td>
<td>P + L,F</td>
<td>90</td>
<td>76</td>
</tr>
<tr>
<td>Pavlin et al.</td>
<td>C 0.15</td>
<td>3</td>
<td>27</td>
<td>T,F</td>
<td>120</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>C 0.2</td>
<td>4</td>
<td>26</td>
<td>T,F</td>
<td>120</td>
<td>96</td>
</tr>
<tr>
<td>Schmautz et al.</td>
<td>C 0.1</td>
<td>2</td>
<td>20</td>
<td>P,F</td>
<td>120</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>C 0.15</td>
<td>3</td>
<td>21</td>
<td>P,F</td>
<td>120</td>
<td>100*</td>
</tr>
<tr>
<td></td>
<td>C 0.2</td>
<td>4</td>
<td>20</td>
<td>P,F</td>
<td>90</td>
<td>75</td>
</tr>
<tr>
<td>Stout et al.</td>
<td>C 0.15</td>
<td>3</td>
<td>20</td>
<td>M,P + L,F</td>
<td>120</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>C 0.1</td>
<td>2</td>
<td>20</td>
<td>M,P + L,F</td>
<td>120</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>C 0.2</td>
<td>4</td>
<td>20</td>
<td>M,P + L,F</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td><strong>Comparison with rocuronium (R)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lien et al.</td>
<td>C 0.4</td>
<td>8</td>
<td>41</td>
<td>M,P,F</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>R 0.9</td>
<td>3</td>
<td>36</td>
<td></td>
<td>M,P,F</td>
<td>60</td>
<td>97</td>
</tr>
<tr>
<td><strong>Dose comparison using different induction agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lien et al.</td>
<td>C 0.15</td>
<td>3</td>
<td>29</td>
<td>M,P,F</td>
<td>90</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>C 0.15</td>
<td>3</td>
<td>30</td>
<td>M,T,F</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>C 0.2</td>
<td>4</td>
<td>28</td>
<td>M,P,F</td>
<td>90</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>C 0.2</td>
<td>4</td>
<td>27</td>
<td>M,T,F</td>
<td>90</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>C 0.3</td>
<td>6</td>
<td>26</td>
<td>M,P,F</td>
<td>90</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>C 0.3</td>
<td>6</td>
<td>28</td>
<td>M,T,F</td>
<td>90</td>
<td>93</td>
</tr>
</tbody>
</table>

a Graded according to a 4-point scale: excellent (easy passage of tube without coughing and vocal cords relaxed and adducted), good (passage of tube with slight cough and/or bucking and vocal cords relaxed and adducted), poor (passage of tube with moderate coughing and/or bucking and vocal cords moderately adducted; results not presented) and not possible (vocal cords tightly adducted).

b The neuromuscular blocker was administered 3 to 5 min after induction of anaesthesia to permit a stable twitch response to be established.

c Nonblinded.

d Abstract.

Abbreviations and symbols: ED95 = dose producing 95% twitch inhibition vs baseline; F = fentanyl; L = lidocaine (lignocaine); M = midazolam; P = propofol; T = thiopental sodium; *p < 0.05 vs other groups; **p < 0.01 vs A.
Table V. Cisatracurium besilate (C) infusion requirements in adults and children undergoing elective surgery and in patients in intensive care.

In patients undergoing elective surgery, infusion of C was administered after a bolus dose(s) and was initiated when T1 had recovered to 5 to 25% of baseline. Recovery data are for spontaneous recovery.

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of pts</th>
<th>Neuromuscular blocker requirements</th>
<th>Maintenance anaesthetics</th>
<th>Recovery (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>infusion rate (µg/kg/min)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>duration&lt;sup&gt;a&lt;/sup&gt;</td>
<td>level of block achieved (%)</td>
</tr>
<tr>
<td>Elective surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belmont et al.</td>
<td>27</td>
<td>C 1.4</td>
<td>109 (11-249) min</td>
<td>≥95</td>
</tr>
<tr>
<td>Mellinghoff et al.</td>
<td>20</td>
<td>C 1.5</td>
<td>122 (78-192) min</td>
<td>≥95</td>
</tr>
<tr>
<td>Oyos et al.</td>
<td>3</td>
<td>C 1.2</td>
<td>100 (83-120) min</td>
<td>≥95</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brandom et al.</td>
<td>7</td>
<td>C 1.8</td>
<td>79 (57-145) min</td>
<td>91-99</td>
</tr>
<tr>
<td>Meretoja et al.</td>
<td>16</td>
<td>C 1.6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>86-99</td>
<td>≥95</td>
</tr>
<tr>
<td>Intensive care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boyd et al.</td>
<td>6</td>
<td>C 3.2 (3-3.3)</td>
<td>28 (24-48)h</td>
<td>91-99</td>
</tr>
<tr>
<td>Prielipp et al.</td>
<td>28</td>
<td>C 2.6 (0.9-6.9)</td>
<td>80 (24-145)h</td>
<td>68&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>V 0.9 (max. 2.3)</td>
<td>66 (12-394)h</td>
<td>387</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mean values (range).
<sup>b</sup> Time taken for T1 to recover from 25 to 75% of baseline.
<sup>c</sup> Abstract.
<sup>d</sup> Calculated requirement from multiple bolus dose data.

Abbreviations and symbols: A = atracurium besilate; E = enflurane; F = fentanyl; H = halothane; I = isoflurane; M = midazolam; max. = maximum; P = propofol; T = thiopental sodium; T1 = first train-of-four response or single twitch; T4 = fourth train-of-four response; V = vecuronium; * p = 0.02 vs V.

3.2 Use in Elective Surgery

Available data describing the use of cisatracurium besilate administered either as a continuous infusion or as repeated bolus doses to facilitate elective surgery are summarised in table V.

3.2.1 Infusion Requirements

In adults anaesthetised with N2O/O2 and an opioid or propofol, the mean infusion rate of cisatracurium besilate required to maintain approximately 95% block ranged from 1.2 to 1.5 µg/kg/min.<sup>[1,4,14]</sup> According to a summary of all available data (total 83 patients), the mean infusion rate required to maintain approximately 95% neuromuscular block is 1.42 (range 0.67 to 2.9) µg/kg/min.<sup>[49]</sup> For atracurium besilate, the mean infusion requirement in the same patient group was 5.3 to 6.6 µg/kg/min, which confirms the greater potency of cisatracurium besilate.<sup>[1,14]</sup> The use of isoflurane or enflurane as part of the maintenance anaesthesia regimen decreased the infusion requirement for cisatracurium besilate by up to one-third;<sup>[41]</sup> infusion recommendations (see section 5) state that reductions of up to 40% may be necessary. Infusion requirements in children (aged 2 to 12 years) were 1.6 and 1.8 µg/kg/min.<sup>[10,16]</sup>

3.2.2 Recovery

After administration of a continuous infusion of cisatracurium besilate, the 25 to 75% recovery index was 15 to 18 minutes in adults and 11 or 14.
minutes in children (table V). In the only study to compare spontaneous recovery after both a single dose and a continuous infusion of cisatracurium besilate, no differences were evident, which suggests that recovery rate is independent of duration of administration.\footnote{27}

As after single-dose administration (section 1.1.2), recovery from neuromuscular block after a continuous infusion or repeated bolus doses of cisatracurium besilate can be effectively accelerated by an anticholinesterase agent. Administration of neostigmine, when neuromuscular transmission had recovered to 11% of baseline, shortened the 25 to 75% recovery index by 14 minutes compared with spontaneous recovery.\footnote{14}

Two studies (total n = 66) also examined the rate of recovery after administration of 1 or more maintenance doses of cisatracurium besilate (0.03 to 0.1 mg/kg).\footnote{29,50} The recovery rate was similar to that observed after a single dose of cisatracurium besilate\footnote{3} and the time to 5% recovery did not appear to alter greatly with increasing numbers of maintenance doses.\footnote{50}

3.3 Use in the Intensive Care Unit

Neuromuscular blocking agents are often administered to patients in intensive care, the most common reason being to assist with mechanical ventilation. Vecuronium, pancuronium and atracurium besilate are commonly used agents in this clinical setting.

Intensive care is a complex environment with the potential for many drug-drug interactions (e.g. with aminoglycoside antibiotics, magnesium salts, calcium channel antagonists) and other conditions (e.g. hypothermia, electrolyte imbalance, acidosis) that potentiate neuromuscular blocking activity. In addition, both the dose and duration of administration of neuromuscular blockers may greatly exceed those used in surgery (days or weeks as opposed to hours).

Two studies have investigated the use of cisatracurium besilate in patients in intensive care (table V).\footnote{29,48} These were a small comparative study with atracurium besilate (n = 12)\footnote{29} and a double-blind, randomised, 5-centre comparison with vecuronium (n = 58).\footnote{48} Neuromuscular blocking agents were administered for at least 12\footnote{48} or 19 hours\footnote{29} in these studies. Where details were provided, the infusion rate was titrated to maintain a TOF count of $\geq 1$\footnote{29,48} and according to patient response (coughing, movement, etc.).\footnote{48}

3.3.1 Infusion Requirements

For adult patients in intensive care, the mean infusion rates of cisatracurium besilate required to maintain adequate neuromuscular block in these studies were 2.6 and 3.2 $\mu$g/kg/min (table V). The largest study, however, reported considerable variation about the mean value [2.6 (range 0.9 to 6.9) $\mu$g/kg/min].\footnote{48} suggesting that the level of neuromuscular block should be monitored regularly and dosage requirements adjusted as needed.

Dosage requirements for cisatracurium besilate remained essentially constant (~2-fold change) over the duration of the infusion in most patients;\footnote{29,48} a ~2-fold increase in requirements was reported in 5 patients (18%) and a ~2-fold decrease in 1 patient (4%) in the study by Prielipp et al.\footnote{48} An infant with multisystem organ failure who received cisatracurium besilate for 40 days showed an 8-fold increase in infusion requirements over this period (2.8 increasing to 22.3 $\mu$g/kg/min).\footnote{51}

3.3.2 Recovery

The mean time to a $T_4 : T_1$ ratio (ratio of the fourth to the first TOF response) of $\geq 0.7$ after an infusion duration of at least 12 hours was 68 ± 13 minutes in cisatracurium besilate recipients (n = 20) versus 387 ± 163 minutes in vecuronium recipients (n = 12; p = 0.02). Two patients who received cisatracurium besilate and 13 vecuronium recipients (p = 0.002) were classified as having a prolonged recovery (assessed subjectively by a blinded investigator), although some patients in each treatment group (10 and 17, respectively) had a TOF count of 0 before discontinuation of infusion.\footnote{48} In addition, all but 4 patients had received a neuromuscular blocking agent (most commonly vecuronium) before initiation of study drug infusion; a retrospective analysis indicated that this was not associated with prolonged recovery. A fur-
ther post hoc analysis revealed that recovery was unaffected by either renal dysfunction or the use of high dose corticosteroids (>300 mg/day).\[48\]

In the only study to measure plasma laudanosine concentrations in this patient group, mean peak concentrations of 710 (range 210 to 1260) µg/L were reported after continuous infusion of cisatracurium besilate (table III).\[29\] Although these values were about 20 to 45 times greater than those reported after a single bolus dose of cisatracurium besilate 0.1 mg/kg (table III), they were approximately 3-fold lower than those observed after a continuous infusion of atracurium besilate [2310 (range 780 to 4400) µg/L] in patients in intensive care.\[29\]

4. Tolerability

In an overview of all clinical trial data (n = 946), adverse events associated with cisatracurium besilate were uncommon and no event was reported with a frequency of > 1%. Events reported as possibly related to cisatracurium besilate and at an incidence of < 1% were bradycardia (0.4%), hypotension (0.2%), flushing (0.2%), bronchospasm (0.2%) and rash (0.1%).\[52\]

In keeping with the haemodynamic profile reported for cisatracurium besilate (section 1.2), no clinically significant haemodynamic events have been reported with the drug in clinical trials.\[7,11,29,43\] Again in clinical trials, no signs of histamine release or flushing were reported in adults (2 to 8 × ED\(_{95}\)),\[3,7,9,19\] children (2 × ED\(_{95}\)),\[12,13,16\] the elderly (2 × ED\(_{95}\))\[53\] or patients with coronary artery disease (2 to 6 × ED\(_{95}\))\[20,21\] after single bolus doses of cisatracurium besilate or in patients in intensive care receiving a continuous infusion of the drug.\[29\]

In comparative studies, flushing was reported in 0% of patients receiving cisatracurium besilate (2 to 4 × ED\(_{95}\)) versus 0 to 11% of patients receiving atracurium besilate (2 × ED\(_{95}\))\[9,15,43\] To date, flushing and mild bronchospasm has been reported in 1 patient after administration of cisatracurium besilate 0.1 mg/kg followed by a continuous infusion.\[44\]

There have been no reports of CNS-related events or cerebral excitation with cisatracurium besilate after single dose administration or after continuous infusion in patients undergoing elective surgery or in intensive care. Investigation of laboratory parameters revealed no evidence of abnormalities in association with cisatracurium besilate.\[13,16\] In a single report of overdose in a 7-month-old infant who received cisatracurium besilate 0.86 mg/kg (= 22 × ED\(_{95}\)), the infant made a complete recovery without any apparent adverse effects.\[17\]

5. Dosage and Administration

Cisatracurium besilate is recommended for intravenous use only. Doses should be individualised and neuromuscular function should be monitored during drug administration, as for any muscle relaxant.

For intubation in adults, cisatracurium besilate 0.15 or 0.2 mg/kg in combination with propofol/N\(_2\)O/O\(_2\) generally produces good to excellent intubating conditions at 2 and 1.5 minutes, respectively. A longer time to achieve satisfactory intubation conditions may be required in elderly patients, in those with renal failure or with lower doses of cisatracurium besilate. In children aged 2 to 12 years, the recommended dose is 0.1 mg/kg administered during halothane or opioid anaesthesia.\[15,21\]

For prolonged surgery, maintenance doses of cisatracurium besilate 0.03 mg/kg are recommended. Each dose maintains neuromuscular block for approximately 20 minutes. In general, maintenance doses are required 40 to 50 minutes and 50 to 60 minutes after initial doses of 0.15 and 0.2 mg/kg, respectively.\[52\] Less frequent or lower maintenance doses may be required during prolonged enflurane or isoflurane anaesthesia. Dosage reductions may also be appropriate in association with sevoflurane anaesthesia.\[112\]

As with other neuromuscular blocking agents, a continuous infusion of cisatracurium besilate should be started only when there is evidence of spontaneous recovery from the initial bolus dose.
Table VI. Summary of the properties of nondepolarising intermediate-acting neuromuscular blocking agents

<table>
<thead>
<tr>
<th>Properties</th>
<th>Cisatracurium besilate</th>
<th>Atracurium besilate</th>
<th>Vecuronium</th>
<th>Rocuronium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuromuscular blocking activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potency(^a)</td>
<td>3-fold greater</td>
<td>1</td>
<td>4- to 5-fold greater</td>
<td>1.3-fold less</td>
</tr>
<tr>
<td>Onset time (min)(^b)</td>
<td>4-6</td>
<td>3-5</td>
<td>3-5</td>
<td>1.5-1.8</td>
</tr>
<tr>
<td>Clinical duration (min)(^b)</td>
<td>35-45</td>
<td>35-45</td>
<td>25-30</td>
<td>31</td>
</tr>
<tr>
<td><strong>Pharmacokinetic properties</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major elimination pathway</td>
<td>Hofmann degradation</td>
<td>Hofmann degradation</td>
<td>Hepatic, renal</td>
<td>Hepatic, renal</td>
</tr>
<tr>
<td>Metabolites</td>
<td>Laudanosine,</td>
<td>Lahudanosine,</td>
<td>3-desacetyl and</td>
<td>17-desacetyl metabolite</td>
</tr>
<tr>
<td></td>
<td>monoquaternary acrylate,</td>
<td>monoquaternary acrylate,</td>
<td>3α-hydroxy metabolites</td>
<td></td>
</tr>
<tr>
<td></td>
<td>monoquaternary alcohol</td>
<td>monoquaternary alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histamine-releasing properties</td>
<td>x</td>
<td>✓(^c)</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Prolonged/residual paralysis</td>
<td>x</td>
<td>x</td>
<td>✓(^d)</td>
<td>x</td>
</tr>
<tr>
<td>Vagolytic effects</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>±</td>
</tr>
</tbody>
</table>

\(^a\) Relative to atracurium besilate.  
\(^b\) Time from end of injection to 95% twitch depression at the adductor pollicis at a dose of 2 × ED95 (dose required to produce 95% suppression of twitch response). All values for balanced anaesthesia.  
\(^c\) At doses >0.5 mg/kg.\(^{[56]}\)  
\(^d\) After long term drug use in intensive care.\(^{[55]}\)  

Symbols: x indicates no or minimal effect; ✓ indicates effect occurs; ± indicates effect may occur.

An initial infusion rate of 3 μg/kg/min is suggested, followed by a rate of 1 to 2 μg/kg/min to maintain 89 to 99% block during opioid/N₂O/O₂ anaesthesia. A 30 to 40% reduction in infusion rate should be considered during stable isoflurane or enfurane anaesthesia, with greater reductions during prolonged anaesthesia. In patients undergoing coronary artery bypass surgery with induced hypothermia, the infusion rate of cisatracurium besilate may need to be reduced by about half, on the basis of data obtained with atracurium besilate.\(^{[52]}\)

In adult patients in intensive care, an infusion rate of 3 (range 0.5 to 10.2) μg/kg/min should provide adequate neuromuscular block. However, there is wide interpatient variation and requirements may vary with time.

As with other neuromuscular blocking agents, caution is warranted in patients with neuromuscular diseases (e.g. myasthenia gravis), in whom prolonged neuromuscular block can occur, and in patients with burns or hemi- or paraparesis, who can develop resistance to these agents. Caution is also required in those with acid-base and/or electrolyte abnormalities. Cisatracurium besilate has not been studied in children aged less than 2 years.

6. Place of Cisatracurium Besilate in Anaesthetic Practice

Several nondepolarising neuromuscular blocking agents with an intermediate duration of action are available; of these, atracurium besilate and vecuronium are the most established in clinical practice. All of these agents have a predictable onset of action and are well tolerated (table VI). Cisatracurium besilate, the newest of this group of drugs, is the R-cis,R'-cis isomer of atracurium besilate and bears many obvious similarities to this agent.

In common with atracurium besilate, cisatracurium besilate has an intermediate clinical duration of action and has a predictable rate of recovery which is independent of dose. Its primary route of elimination is by Hofmann degradation. For this
reason, cisatracurium besilate, like atracurium besilate, is not associated with prolonged recovery in patients with renal dysfunction or in those with end-stage liver disease. In terms of potency, cisatracurium besilate is approximately 3-fold more potent than atracurium besilate in humans (when comparing doses expressed as the cation). However, in keeping with the generally accepted hypothesis that neuromuscular blocking potency is inversely related to speed of onset, cisatracurium besilate has a slightly slower onset of action than atracurium besilate at equipotent doses (table VI). Cisatracurium besilate is not associated with dose-related histamine release at doses of up to and including \(8 \times \text{ED}_{95}\). In keeping with this, early assessments of the cardiovascular effects of cisatracurium besilate in healthy adults and those with underlying cardiovascular disease have been promising; however, more clinical experience is required. Issues of relative cost are beyond the scope of this review but are discussed in detail by Colosimo and Levon.

An issue of concern with atracurium besilate in intensive care relates to its primary breakdown product by Hofmann degradation, laudanosine. Laudanosine produces seizures in animals at high plasma concentrations (17 000 \(\mu\text{g/L}\)). However, the relationship between laudanosine concentrations and CNS effects in humans, if any, has not been established. Concentrations of laudanosine reported after prolonged administration of atracurium besilate in patients in intensive care range from 520 to 8650 \(\mu\text{g/L}\) (table III). While there have been rare reports of seizures in patients receiving atracurium besilate in an intensive care setting, no adverse event has been definitely attributed to laudanosine accumulation. Cisatracurium besilate, by way of its lower dosage requirements relative to atracurium besilate, is associated with lower laudanosine concentrations after single dose and prolonged administration (table III). Therefore, any risk associated with laudanosine would seem to be even less with cisatracurium besilate than with atracurium besilate.

Cisatracurium besilate, like atracurium besilate, when given as a single dose appears to be an attractive choice for surgical procedures of between 30 and 60 minutes, or for longer procedures when administered as a continuous infusion or by repeat bolus doses. In longer procedures, intermediate-acting agents may be preferable to longer-acting agents because patients recover more rapidly. Cisatracurium besilate, by way of its organ-independent elimination, is likely to be favoured over vecuronium and rocuronium in patients with renal or hepatic disease. However, no comparative trials with other intermediate-acting agents have yet been performed and there are no multiple-dose data with cisatracurium besilate in patients with end-organ disease.

For intubation, good or excellent conditions can be achieved 90 to 120 seconds after a 0.15 or 0.2 \(\text{mg/kg}\) dose of cisatracurium besilate after induction with propofol or thiopental sodium. More consistent results were obtained at 90 seconds when midazolam was included in the induction regimen. In this setting, the slower onset of action of cisatracurium besilate means that it will not compete with suxamethonium chloride for emergency or rapid sequence intubation.

Cisatracurium besilate, like atracurium besilate, is likely to be a useful agent in intensive care because of its organ-independent metabolism and predictable recovery. When compared with vecuronium in patients in intensive care, cisatracurium besilate was associated with a significantly faster recovery after continuous infusions lasting at least 12 hours.

In conclusion, the properties of cisatracurium besilate indicate that it is an attractive intermediate-acting neuromuscular blocking agent. Relative to atracurium besilate, the only agent to which it has been consistently compared, cisatracurium besilate has a lower propensity to cause histamine release and is more potent but has a slightly longer onset time at equipotent doses. After prolonged administration, cisatracurium besilate offers a more predictable recovery profile than vecuronium in patients in intensive care. Therefore, available...
comparative data provide some indication of the potential of this agent but further comparisons with other like agents are required to define precisely the relative merits of cisatracurium besilate.

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