The Incidence of hypotension with continuous infusion atracurium compared to cisatracurium in the Intensive Care Unit

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ABSTRACT

Background: A drug shortage of cisatracurium led to use of atracurium as an alternative neuromuscular blocker (NMB). Cisatracurium may be preferred due to less histamine release and potentially less hypotension. The study purpose is to compare the incidence of hypotension with continuous infusion atracurium to continuous infusion cisatracurium in ICU patients.

Materials and Methods: This retrospective cohort analysis reviewed 119 ICU patients who received either continuous infusion atracurium (56) or cisatracurium (63). The primary outcome was the incidence of hypotension (mean arterial pressure <60mmHg). Secondary outcomes included: incidence of blood pressure decrease of >20% from baseline, time to first hypotensive episode, treatment for hypotension during NMB use, hospital mortality, ICU and hospital length of stay (LOS), duration of mechanical ventilation (MV), and NMB duration.

Results: Hypotension occurred in 64.3% of atracurium patients and 58.7% of cisatracurium patients (P = 0.58), with 60.7% experiencing >20% drop in blood pressure in atracurium group and 54.0% in cisatracurium (P = 0.58). Median time to first hypotensive episode was 9.4[Interquartile range 1.17-19.7] hours atracurium and 4.4[1.5-13.9] hours cisatracurium (P = 0.36). There were no differences between atracurium and cisatracurium groups respectively for median ICU LOS (10.5 days and 12.4 days, P = 0.34), hospital LOS (14.0 days and 17.7 days, P = 0.37), MV duration (9.3 days and 10.5 days, P = 0.43), infusion duration (34.5 hours and 25 hours P = 0.27), or hospital mortality (62.5% and 53.9%, P = 0.336). Hypotension treatment was similar between groups.

Conclusions: The incidence of hypotension was similar between atracurium and cisatracurium. Critical drug shortages may provide an opportunity to study alternative drug therapy.

Key Words: Adverse drug reactions, antihistamine, critical care, hemodynamics, neuromuscular blocker

INTRODUCTION

Atracurium and cisatracurium are benzylisoquinolinium nondepolarizing neuromuscular blocking agents (NMB) that are inactivated by plasma hydrolysis and Hofmann elimination. As a result, they do not accumulate in patients with hepatic and/or renal insufficiency, making them useful in critically ill patients.[1,2] Atracurium has...
been associated with a decrease in mean arterial pressure (MAP) of up to 30 mmHg within 2 min of initiation, which could result in hypotension and may be associated with histamine release. It is unclear if this effect is due to atracurium causing histamine release alone or a combination of the other agents used for induction of sedation. Most of the hemodynamic effects of atracurium seem to be associated with the initial infusion, and it is unknown if these hemodynamic effects persist when atracurium is used as a continuous infusion. A histamine 1 (H1) receptor antagonist and a histamine 2 (H2) receptor antagonist are often used to attenuate histamine release and help prevent this cardiovascular side effect.

Cisatracurium is an R-cis-R’-cis isomer of atracurium. It is a potent neuromuscular blocker and has been touted for its ability to provide therapeutically equivalent neuromuscular blockade without affecting blood pressure or heart rate, possibly due to its lack of effect on histamine release.

In January 2014, due to a drug shortage of cisatracurium, atracurium was added to the formulary of accepted medications during the shortage and was used until September 2014 when the supply of cisatracurium returned to acceptable levels. The purpose of this study is to compare the incidence of hypotension in critically ill patients receiving continuous infusion atracurium or continuous infusion cisatracurium.

METHODS

Data collection and analysis
The University Institutional Review Board approved this two-hospital health system, retrospective cohort study to compare the rates of hypotension in Intensive Care Units (ICUs) patients treated with continuous infusion atracurium or cisatracurium in accordance with the ethical standards set forth in the Helsinki Declaration on 1975.

Patients were evaluated for inclusion if they were in either the medical, surgical, neurosciences, or cardiac ICU at a University Medical Center or in the mixed medical/surgical ICU at a University Affiliated Community Hospital and received either continuous infusion atracurium between January 1, 2014, and September 20, 2014 or cisatracurium between January 1, 2013, and September 20, 2013. Patients were excluded from the study if they were under 18-year-old, over 89-year-old, had baseline MAP <60 mmHg, or were incarcerated.

The primary outcome was the incidence of hypotension, defined as a MAP <60 mmHg, in patients receiving continuous infusion atracurium compared to cisatracurium. Secondary outcomes included the incidence of blood pressure decrease of >20% from baseline, time to first hypotensive episode, number of hypotensive events, incidence of treatment for hypotension during NMB use, hospital mortality, ICU and hospital length of stay, duration of mechanical ventilation, and paralytic duration.

Baseline demographic data collected included: gender, age, weight, height, primary service caring for the patient, blood urea nitrogen (BUN), serum creatinine, Acute Physiologic and Chronic Health Evaluation II (APACHE II) score within 24 h of ICU admission, and past medical history. A study data collected for NMB use included: NMB dosing and length of NMB infusion duration. To determine the potential NMB hemodynamic effects and eliminate areas of confounding, antihypertensive, vasopressor, and inotropic medication use before and during NMB infusion was evaluated. Baseline MAP and heart rate immediately before NMB initiation was collected to compare the two groups. To evaluate the primary endpoint, the total number of hypotensive incidents for each patient and method of treating any hypotensive episodes (fluid bolus or initiation or titration of hemodynamic medication) was collected. The use of an H1 and/or H2 agent before NMB initiation (as pretreatment or home or hospital use) was evaluated to control for the effects of histamine on the incidence of hypotension. Clinical outcomes data collected included: hospital mortality, length of hospital and ICU stay, and mechanical ventilation duration.

Statistical analysis
Given the retrospective, observational nature of this study and lack of prior studies to develop an estimate of the incidence of hypotension with continuous infusions of cisatracurium and atracurium, no power calculations were performed to determine sample size. Continuous data were analyzed using either t-test for parametric data and presented as mean ± standard deviation or Wilcoxon test for nonparametric data and presented as median (25%–75% interquartile range). Categorical data were analyzed using either Chi-square test or Fisher’s exact test. A multivariate logistic regression analysis was conducted for patients with and without hypotension following univariate analysis. Risk factors significant with a \( P < 0.25 \) and occurred before the initiation of NMB were considered for inclusion is a stepwise backward regression model. Results are reported as adjusted odds ratio (OR) with corresponding 95% confidence intervals (CIs). A two-sided \( P < 0.05 \) was considered to be statistically significant. Statistical analyses were performed using SPSS for Windows (version 21, IBM, Armonk, NY, USA).
RESULTS

A total of 152 patients were screened for inclusion in the study. A total of 119 were included for analysis with 56 patients receiving continuous infusion atracurium and 63 patients receiving continuous infusion cisatracurium [Figure 1]. Thirty-three patients were excluded, 16 did not receive a continuous infusion of the study medication, eight patients that had baseline MAP <60 mmHg, five patients had incomplete charting data, and four patients were incarcerated. The majority of patients that received continuous infusion NMB were male (63%) with a median APACHE II of 33 (26–38). Approximately, half of patients were in the medical ICU and one-fourth in the surgical ICU. There were no significant differences in the baseline demographics between the two groups [Table 1].

There was not a significant difference in the use of a loading dose (atracurium, 75% vs. cisatracurium, 65.1%, P = 0.24) or median length of infusion between groups (atracurium, 34.5 [12.3–73.6] h vs. cisatracurium, 25 [11.8–62.8] h, P = 0.27) [Table 2].

Hypotension (MAP <60 mmHg) was common with 64.3% of patients experiencing at least one hypotensive episode while receiving continuous infusion atracurium compared to 53.9% of patients in the cisatracurium group (P = 0.58). For the secondary outcomes, the median time to the first hypotensive episode was similar between groups (atracurium, 9.4 h [1.17–19.7] h vs. cisatracurium, 4.4 h [0.73–19.9], P = 0.35). For those that developed hypotension, the median nadir MAP was 50.5 mmHg (45–55) for the atracurium group and 54 mmHg (48–57) for the cisatracurium group, P = 0.20. The median number of hypotensive events was similar (atracurium, 2 [0–5] vs. cisatracurium, 1 [1–3], P = 0.16). A similar percentage of patients in each group had a ≥20% decrease in their MAP (atracurium, 60.7% vs. cisatracurium, 53.9%, P = 0.58).

Overall, the use of concurrent histamine blockers was low with 34.6% of all patients receiving one, including 35.6% in the atracurium group, and 33.8% in the cisatracurium group, P = 0.83. As a cohort, 64% of patients that did not receive a histamine blocker had a MAP <60 mmHg while 61% of patients that did receive a histamine blocker experienced hypotension, P = 0.85. Of the patients that received a histamine blocker, there was not a significant difference in the rate of hypotension between the two groups (atracurium, 57% vs. cisatracurium, 65%, P = 0.76). Conversely, the majority of patients in both groups received a loading dose of the NMB (atracurium, 74.6% vs. cisatracurium, 60.7%, P = 0.76).

![Diagram showing inclusions and exclusions](image)

**Figure 1:** Inclusions and exclusions flow diagram

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### Table 1: Baseline demographics of atracurium and cisatracurium patients

| Characteristic | ATRA group (n = 56) | CIS group (n = 63) | P |
|---------------|-------------------|------------------|---|
| Mean age (years) | 51.5 ± 14.2 | 53.3 ± 15.4 | 0.91 |
| Male, n (%) | 35 (62.5) | 40 (63.5) | 0.58 |
| Median weight (kg) | 90.2 (71.4-103.6) | 91.4 (77.1-122.9) | 0.28 |
| Past medical history, n (%) | | | |
| Liver disease | 7 (13) | 8 (13) | >0.99 |
| Renal disease | 6 (11) | 4 (6) | 0.51 |
| CHF | 7 (13) | 7 (11) | 0.99 |
| Median baseline MAP (mmHg) | 71.5 (66-80) | 75 (66-82) | 0.31 |
| Mean baseline heart rate (bpm) | 102 ± 21.2 | 108 ± 24.1 | 0.12 |
| Median BUN (mg/dL) | 29.5 (20.5-45.5) | 24.5 (17-39) | 0.20 |
| Median Scr (mg/dL) | 1.47 (0.91-2.28) | 1.33 (0.84-1.83) | 0.37 |
| Patient location, n (%) | | | |
| MICU | 31 (55) | 28 (44) | 0.27 |
| SICU | 14 (25) | 19 (30) | 0.55 |
| Neurosciences | 1 (2) | - | 0.48 |
| Cardiac | 4 (7) | 6 (10) | 0.75 |
| Mixed MICU/SICU | 6 (11) | 10 (16) | 0.44 |
| Median APACHE II | 34 (25.5-38) | 32.5 (28-41) | 0.67 |

Presented as mean ± SD and median (25%–75% IQR). ATRA: Atracurium, n: Number of patients, CIS: Cisatracurium, CHF: Congestive heart failure, MAP: Mean arterial pressure, ICU: Intensive Care Unit, SICU: Surgical Intensive Care Unit, APACHE II: Acute Physiology and Chronic Health Evaluation II, SD: Standard deviation, BUN: Blood urea nitrogen, SCR: Serum creatinine

### Table 2: Comparison of outcomes in atracurium and cisatracurium patients

| Characteristic | ATRA group (n = 56) | CIS group (n = 63) | P |
|---------------|-------------------|------------------|---|
| Primary outcome, n (%) | | | 0.58 |
| MAP < 60 mmHg | 36 (64.3) | 37 (58.7) | |
| Secondary outcomes | | | 0.58 |
| MAP ≥20% decrease, n (%) | 34 (60.7) | 34 (53.9) | |
| Time to MAP < 60 mmHg (h) | 9.4 (1.17-19.7) | 4.4 (1.5-13.9) | 0.36 |
| Nadir MAP (mmHg) | 50.5 (45-55) | 54 (48-57) | 0.20 |
| Number of events (MAP < 60 mmHg) | 2 (0-5) | 1 (1-3) | 0.16 |
| Hospital mortality, n (%) | 35 (62.5) | 34 (53.9) | 0.36 |
| Mechanical ventilation duration (days) | 9.3 (3.3-20) | 10.5 (5.9-17.7) | 0.43 |
| Hospital length of stay (days) | 14.0 (6.7-26.7) | 17.7 (9.0-25.5) | 0.37 |
| ICU length of stay (days) | 10.5 (3.6-23.6) | 12.4 (7.8-19.9) | 0.34 |
| Time to ICU admission (h) | 2.2 (0-18.2) | 1.4 (0-13.8) | 0.35 |

Reported as n (%) or median (IQR). ATRA: Atracurium, n: Number of patients, CIS: Cisatracurium, MAP: Mean arterial pressure, ICU: Intensive Care Unit, IQR: Interquartile range
The use of a loading dose was not associated with a significant difference in hypotension rates (loading dose, 54% vs. no loading dose, 67%, \( P = 0.17 \)). Patients that received a loading dose did not have a difference in the rate of hypotension between the two groups (atracurium, 67% vs. cisatracurium, 66%, \( P = 0.99 \)).

Clinical outcomes assessed were similar between the two groups [Table 2]. Median ICU length of stay (atracurium, 10.5 days [5.7–25.6] vs. cisatracurium, 12.2 days [7.3–19.4], \( P = 0.31 \)), median hospital length of stay (atracurium, 14 days [5.7–25.6] vs. cisatracurium, 17.9 days [9–25.5], \( P = 0.29 \)), and median duration of mechanical ventilation (atracurium, 9.3 days [2.9–19.8] vs. cisatracurium, 10.3 days [5.6–18.4], \( P = 0.37 \)) were also similar between the groups. The overall hospital mortality rate was high in both groups (atracurium, 64% compared to cisatracurium, 56%, \( P = 0.33 \)).

While the majority of patients were on antihypertensive agents before hospitalization (atracurium, 64% vs. cisatracurium, 67%, \( P = 0.79 \)), only 31% of both atracurium patients and cisatracurium patients received an antihypertensive agent prior to the NMB, \( P = 0.99 \) [Table 3]. A similar number of patients received an antihypertensive during the NMB infusion (atracurium, 31% vs. cisatracurium, 41%, \( P = 0.24 \)). Before NMB initiation, 69% of atracurium patients and 56% of cisatracurium patients were on a vasopressor or inotrope, \( P = 0.13 \). Hypotension occurred in 76% of those receiving a vasopressor and inotrope and atracurium compared to 71% of those receiving cisatracurium and vasopressor or inotrope, \( P = 0.79 \). The majority of patients received at least one treatment for hypotension while on NMB (atracurium, 71% vs. cisatracurium, 72%, \( P = 0.91 \)). The most common treatment was increasing the dosage of vasopressor (atracurium, 54% vs. cisatracurium, 57%, \( P = 0.72 \)), followed by fluid bolus (atracurium, 44% vs. cisatracurium, 40%, \( P = 0.62 \)), and initiating a new vasopressor (atracurium, 27% vs. cisatracurium, 34%, \( P = 0.41 \)).

Factors entered into multivariate analysis were baseline heart rate and BUN, use of a histamine blocker, diuretic or dihydropyridine calcium channel blocker before hospitalization, administration of a loading infusion and use of a vasopressor and/or inotrope during hospitalization before NMB initiation. The multivariable logistic analysis only identified prior vasopressor and/or inotrope as independent risk factors for the development of hypotension. The adjusted OR was 3.7 (95% CI: 1.6–8.5, \( P = 0.002 \)) with a Hosmer–Lemeshow goodness-of-fit test \( P = 0.5 \).

**DISCUSSION**

Overall, the incidence of hypotension occurred in approximately two-thirds in patients receiving continuous atracurium or cisatracurium and did not significantly differ between groups. A similar percentage of patients had a ≥20% decrease in MAP from baseline after NMB was initiated. In multivariable analysis, the odds of hypotension increased over 3 times for those already receiving vasopressors and/or inotropes prior to initiation of NMB. Approximately, 70% of patients in each group required some sort of hemodynamic support (vasopressor titration or initiation and fluid bolus), essentially forming a surrogate marker of hypotension. This high rate of hypotension is not uncommon among critically ill patients, and has been associated with an increased mortality, length of hospital and ICU stay, and cardiac damage among various populations.\(^{11-14}\) As this study focused on individuals receiving NMBs, it is to be expected that the population would represent real-world patients who are more acutely critically ill. The multivariable analysis shows these patients may already be at higher risk for hypotension as over half of the patients were already receiving a vasopressor or inotrope prior to initiation of NMB. The high mortality rate in this study also reflects the severity of illness in these patients as measured by the high median APACHE II scores. The development of NMB associated hypotension seen may be a result of the patient population they are used in rather than an impact of either drug.
The use of concurrent medications during continuous NMB use may compounding any hemodynamic effect due to the NMB alone. The recently published 2016 Clinical Practice Guidelines for Sustained Neuromuscular Blockade in the Adult Critically Ill Patient recommend administering analgesic and sedative drugs (often opioids and benzodiazepines) prior to and during NMB with goal of deep sedation.[13] Agents in both of these drug classes have been associated with hypotension in critically ill patients.[16-22] Doenicke et al. demonstrated that when the induction agents are separated from atracurium administration by several minutes, hypotension does not occur.[5] These results suggest that atracurium alone may not be the cause of hypotension, but that the risk is compounded by other drug and nondrug factors.[5,16]

Our study suggests that despite these factors, critically ill patients at high risk for hypotension, atracurium use may not increase the risk further compared to cisatracurium use.

It has been proposed that histamine release may also contribute to hypotension especially with bolus dose atracurium.[4,15] Several studies have demonstrated that this increase in histamine release is associated with a high dose or rapid infusion of atracurium and have also demonstrated that the combined use of an H1 and H2 antagonist can attenuate this response.[3,8,15] In addition, a trial by Scott et al. demonstrated that giving the bolus infusion of atracurium over 75 s abolished the hemodynamic effects seen with a rapid (5 s) bolus infusion.[9] As cisatracurium has not been associated with this phenomenon, it was necessary to identify which patients may have gotten a loading dose, increasing their risk of histamine release, or may have been on agents that could have decreased histamine release (i.e., H1 or H2 receptor antagonists).[3,8] A strength of our study was the care taken to control for these dosing variables that may have contributed to hypotension or prevented it. However, due to the retrospective design, we could not document the rate of the bolus infusion. In our results, there does not appear to be a significant difference in the rate of hypotension in patients who received a loading dose (atracurium, 67% vs. cisatracurium, 66%), and this is comparable to the approximately two-thirds of patients who experienced hypotension in each group. While approximately a third of patients in each group received a histamine release blocker, rates of hypotension were similar (atracurium, 57% vs. cisatracurium, 65%). Therefore, the development of hypotension in critically ill patients receiving continuous atracurium or cisatracurium may not be a result of histamine release.

This study does have limitations. As it is retrospective in nature, a causal relationship cannot be determined. In particular, we did not track ventilator changes such as increases in positive end-expiratory pressure which potentially can cause a decrease in MAP. As stated earlier with our documentation system it is impossible to know how quickly loading boluses were administered. Small sample size is also a limitation, but this was unavoidable given the limited population that received atracurium during the study period. Finally, the volume status of the patients was unable to be determined in this retrospective study. Despite these limitations, this trial does provide some evidence that atracurium may not be associated with a higher risk of hypotension compared to cisatracurium in a clinical ICU setting.

CONCLUSIONS

Overall, approximately, two-thirds of patients that received continuous NMB in an ICU developed hypotension. The rate of hypotension was similar for patients receiving continuous infusion atracurium compared to continuous infusion cisatracurium. More studies are needed to further evaluate this risk and guide clinical practice.

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Conflicts of interest
There are no conflicts of interest.

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