Influence of acute normovolaemic haemodilution on the dose–response relationship and time course of action of cisatracurium besylate

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Background. Acute normovolaemic haemodilution (ANH) is an efficacious blood conservation strategy aiming at avoiding allogeneic blood transfusion. ANH was shown to increase the potency of vecuronium, atracurium, and rocuronium. The aim of our study was to investigate whether cisatracurium potency is altered with ANH.

Methods. Using the Relaxometer mechanomyograph, we compared cisatracurium dose–response relationship and time course of action in 60 patients randomly allocated to the ANH or control groups. Patients in each group were randomly allocated to receive one of three cisatracurium doses (30, 40, 50 µg kg⁻¹) followed by a second supplemental dose to reach a total of 100 µg kg⁻¹.

Results. ANH did not result in a significant shift in cisatracurium log dose–probit dose–response curve. There was no significant difference in mean (95% confidence intervals) ED₅₀, ED₉₀, and ED₉₅ (effective doses required for 50, 90, and 95% first twitch depression) between the ANH group [29.5 (27–32), 50.4 (47.4–53.4), 58.7 (55.3–62) µg kg⁻¹] and the control group [28.2 (25.3–31), 47.6 (44.9–50.3), 55.3 (52.5–58.1) µg kg⁻¹], whereas there was no difference in mean (SD) Dur₂₅ and Dur₀.₈ (time until 25% first twitch and 0.8 train-of-four ratio recoveries) between the ANH group [40.8 (5.9), 64.7 (8.4) min] and the control group [42.2 (7.6), 66.5 (10.7) min].

Conclusions. Our results demonstrated that unlike other previously reported neuromuscular blocking drugs, ANH did not alter cisatracurium potency. Thus, cisatracurium would be the neuromuscular blocking drug of choice in patients who undergo surgery with ANH, as no dose adjustments are required.


Keywords: monitoring; neuromuscular block; neuromuscular blocking agent

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with ANH. We assessed cisatracurium’s dose–response relationship and time course of action in patients undergoing surgery with and without ANH.

**Patients and methods**

A prospective, controlled, clinical, consecutive study was conducted in conformity with the guidelines of ‘Good clinical research practice (GCRP)’ in pharmacodynamic studies of neuromuscular blocking agents’ and the ‘Consolidated standards of reporting trials (CONSORT) statement’.

After ethics committee approval, all patients who agreed to participate in the study gave written informed consent. Exclusion criteria were history of neuromuscular disease, small joint arthritis, haemoglobin (Hb) less than 12 g dl⁻¹, body mass index of less than 20 or more than 26 kg m⁻², or treatment with drugs thought to interfere with neuromuscular transmission.

Based upon a previous study, our a priori power analysis showed that a subgroup size of 10 patients would be required to reveal a statistically significant difference between the two groups. Using a computer-generated randomization list, 60 patients with American Society of Anesthesiologists (ASA) classification I–III undergoing radical cystectomy, radical hysterectomy, or retropubic radical prostatectomy were randomly allocated to the ANH or control groups and were stratified by gender and ASA classification. Patients in each group were randomly allocated to receive one of three initial cisatracurium doses (30, 40, 50 μg kg⁻¹), followed by a second supplemental dose to reach a total dose of 100 μg kg⁻¹.

A radial artery cannula was placed under local anaesthetic, before anaesthesia induction. Arterial Hb, haematocrit (Hct), and total plasma proteins were measured before anaesthesia induction. Arterial Hb, haematocrit, before anaesthesia induction. Arterial Hb, haematocrit, and after ANH. A volume of 15 ml kg⁻¹ of the operation after the phase of major blood loss, or if the Hb less than 7 g dl⁻¹ was administered into a rapidly running infusion and the maximum neuromuscular block, defined as three consecutive T₁ responses that did not register a decline, was recorded. Cisatracurium dose–response curves were obtained according to Donlon’s single-dose method using the ordinary least-squares regression of the probit transformation of T₁ maximum twitch suppression against the common logarithm of each dose. Mean regression lines representing the two groups were plotted using the slopes and intercepts, from which the doses required for 50, 90, and 95% T₁ depression (ED₅₀, ED₉₀ and ED₉₅, respectively) were calculated.

This was followed by a second supplemental dose to reach a total dose of 100 μg kg⁻¹. Patients were allowed to recover spontaneously from the neuromuscular block. Duf₂₅ (time from beginning of cisatracurium first dose administration until 25% T₁ recovery), Duf₂₅–₇₅ (time from 25 to 75% T₁ recovery), Duf₂₅–₀₈ (time from 25% T₁ to 0.8 TOF ratio recovery), and Duf₀₃ (time from beginning of cisatracurium first dose administration until 0.8 TOF ratio recovery) time course of action variables were calculated.

**Statistical analysis**

The primary endpoint of our study was to compare cisatracurium ED₉₅ in patients who underwent ANH with control subjects. Based upon a previous study, in which atracurium ED₉₅ was 208 (37) μg kg⁻¹ in patients who underwent ANH and 309 (88) μg kg⁻¹ in control subjects, our a priori power analysis (α=0.05) with 101 (51) μg kg⁻¹ difference between the two groups, showed that a subgroup size of 10 patients would be required to reveal a statistically significant difference between the two groups with >80% power. Analysis of covariance (two-way ANOVA) was used for intergroup analysis. Data were expressed as means (sd or 95% confidence intervals). P<0.05 was considered statistically significant.
Results

Patients’ characteristics are presented in Table 1. There was no significant blood loss during the neuromuscular monitoring period of the study. Haemoglobin, Hct, and plasma proteins declined significantly with ANH (Table 1). There were no significant differences between the two groups in the T1 stabilization period, anaesthesia induction period, skin and core temperature, mean arterial pressure, estimated blood loss, fluid replacements, and propofol and remifentanil requirements during the neuromuscular monitoring period of the study.

Our study showed that ANH did not result in a significant shift in the cisatracurium dose–response curve (Fig. 1). There were no significant differences between the two groups in cisatracurium onset time or maximum T1 block (Table 2). Although cisatracurium ED50, ED90, and ED95 were slightly higher in the ANH group indicating a minor decrease in potency, still the differences between the two groups did not reach statistical significance (Table 3). The duration of action (Dur25 and Dur0.8) and the rate of recovery (Dur25–75, Dur25–0.8) parameters were similar between the two groups (Table 4).

Discussion

The principal dose–response relationship finding of our study was that unlike other previously reported neuromuscular blocking drugs, in which ANH was shown to increase their potency thus requiring lower doses,4–7 ANH did not significantly alter the potency of cisatracurium as evident by the similar ED50, ED90, and ED95 in the two groups. Although we did not specifically assess the above-mentioned neuromuscular blocking drugs under the exactly same ANH conditions, we can speculate that the observed differences between cisatracurium and other neuromuscular blocking drugs including atracurium could arise from their significantly different distribution characteristics, because dose–response relationships depend mainly on the initial concentration of a drug rather than the disposition process that follows. Cisatracurium is only 1 of the 10 stereoisomers that constitute atracurium and makes up just 15% of the atracurium mixture.13 Smith and colleagues13 demonstrated that cisatracurium possesses a significantly different distribution profile than the other three geometric isomer groups that constitute the atracurium mixture.13 Furthermore, atracurium’s volume of distribution at steady state (Vdss) and distribution half-life (t1/2a) [87.4 (31) ml kg⁻¹, 2.1 (0.4) min]14 15 are different from cisatracurium’s Vdss and t1/2a [168 (44) ml kg⁻¹, 6.4

![Fig 1](image_url) Cisatracurium log dose–probit curves (upper and lower 95% confidence intervals) in the acute normovolaemic haemodilution (ANH) and control groups.

<table>
<thead>
<tr>
<th>Blood investigations</th>
<th>Before ANH</th>
<th>After ANH</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g dl⁻¹)</td>
<td>13.6 (0.9)</td>
<td>8.7 (1.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>41.7 (2.5)</td>
<td>28.6 (4.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plasma proteins (g dl⁻¹)</td>
<td>6.7 (0.8)</td>
<td>4.4 (0.4)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 1 Patients’ characteristics and blood investigations. Means (SD or range). ANH, acute normovolaemic haemodilution; BMI, body mass index; Hb, haemoglobin; Hct, haematocrit.
Cisatracurium and acute normovolaemic haemodilution

Table 2 Time to T1 baseline stabilization, anaesthesia induction, cisatracurium onset, and maximum T1 block. Means (SD), n=30. ANH, acute normovolaemic haemodilution; onset time, time from beginning of cisatracurium first dose administration until first response of train-of-four (T1) maximum suppression

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Control group</th>
<th>ANH group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 baseline stabilization</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Anaesthesia induction</td>
<td>3 (2)</td>
<td>3 (1)</td>
<td></td>
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</tbody>
</table>

Onset time (min)

<table>
<thead>
<tr>
<th>Cisatracurium µg kg⁻¹</th>
<th>Control group</th>
<th>ANH group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>7.0 (1.5)</td>
<td>6.6 (2.0)</td>
<td>0.6270</td>
</tr>
<tr>
<td>40</td>
<td>7.2 (2.4)</td>
<td>7.0 (2.1)</td>
<td>0.8478</td>
</tr>
<tr>
<td>50</td>
<td>6.3 (2.1)</td>
<td>6.0 (1.8)</td>
<td>0.7391</td>
</tr>
</tbody>
</table>

Maximum T1 block (%)

<table>
<thead>
<tr>
<th>Cisatracurium µg kg⁻¹</th>
<th>Control group</th>
<th>ANH group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>60.8 (7.4)</td>
<td>59.6 (7.9)</td>
<td>0.7299</td>
</tr>
<tr>
<td>40</td>
<td>78.0 (6.0)</td>
<td>74.5 (7.1)</td>
<td>0.2495</td>
</tr>
<tr>
<td>50</td>
<td>88.9 (4.8)</td>
<td>85.1 (3.8)</td>
<td>0.0655</td>
</tr>
</tbody>
</table>

Table 4 Cisatracurium time course of action. Means (SD), n=30. ANH, acute normovolaemic haemodilution; Dur25, time from beginning of cisatracurium first dose administration until first response of train-of-four (T1) 25% recovery; Dur25–75, time of T1 recovery from 25 to 75%; Dur25–0.8, time from beginning of cisatracurium first dose administration until 0.8 train-of-four ratio recovery; Dur25–0.8, time from T1 25% until 0.8 train-of-four ratio recovery

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group</th>
<th>ANH group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dur25 (min)</td>
<td>42.2 (7.6)</td>
<td>40.8 (5.9)</td>
<td>0.1758</td>
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<tr>
<td>Dur25–75 (min)</td>
<td>12.3 (2.6)</td>
<td>11.9 (2.2)</td>
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<tr>
<td>Dur25–0.8 (min)</td>
<td>24.3 (7.6)</td>
<td>23.9 (8.1)</td>
<td>0.6269</td>
</tr>
<tr>
<td>Dur0.8 (min)</td>
<td>66.5 (10.7)</td>
<td>64.7 (8.4)</td>
<td>0.7669</td>
</tr>
</tbody>
</table>

(0.5) min].² ¹³ Whereas, the previously reported succinylcholine,⁴ pancuronium,⁴ vecuronium,⁵ and rocuronium⁷ were either depolarizing⁴ or aminosteroid neuromuscular blocking drug,⁴ ⁵ ⁷ all with distribution features completely different from cisatracurium.

In our study, Hct declined to 28.6 (−31%), indicating significant haemodilution. A recent study in patients who underwent ANH with HES demonstrated that haemodilution fluids increased the extracellular fluid volume by 600–800 ml;¹⁶ this would consequently result in cisatracurium dilution as cisatracurium is rapidly distributed into the extracellular space.¹⁵ Unlike other neuromuscular blocking drugs in which ANH was shown to significantly increase their potency and shift their dose–response curves to the left,⁴ ⁵ ⁷ in our study, cisatracurium’s dose–response curve was actually shifted to the right, indicating a decrease, albeit not statistically significant, in its potency (Fig. 1, Table 3). This could be attributed to the fact that because ANH did not significantly influence the potency of cisatracurium, our dose–response curve just reflected the initial dilution of cisatracurium plasma concentrations.

The principal time course of action finding of our study was that cisatracurium’s duration of action (Dur 25–75) and recovery rate parameters (Dur 25–0.8) were not prolonged in the ANH group compared with the control group. However, Xue and colleagues⁶ showed that ANH prolonged atracurium’s time course of action. In addition to the fact that recovery parameters are crude measurements of the elimination process and might not detect minor differences between groups, still the differences between cisatracurium and atracurium could be attributed to the differences in the disposition process. Fisher and colleagues¹⁴ found that more than 60% of atracurium clearance was organ-based through pathways other than Hofmann degradation and ester hydrolysis.¹⁴ Although, cisatracurium retained atracurium’s advantage of spontaneous organ-independent, base catalysed, temperature-dependent Hofmann degrada-
tion, but unlike atracurium, cisatracurium is not eliminated via the non-specific plasma esterases hydrolysis pathway.⁵ The clinical implications of our results are that no adjustment in cisatracurium’s initial and repeat doses is necessary in patients who undergo surgery with ANH.

The protein bound fraction of cisatracurium was recently reported to be 38%.¹⁷ In our study, there was a significant decline in total plasma proteins with ANH. The decreased protein-binding capacity could have purportedly resulted in higher concentrations of cisatracurium’s pharmacologically active free fraction. However, plasma protein-binding changes were recently shown to have little clinical relevance.¹⁸ Benet and Hoener¹⁸ demonstrated that except drugs with very high extraction ratio, changes in plasma protein binding do not influence the clinical exposure of a patient to parenterally administered drugs such as cisatracurium. They found that the concept that effective concentrations of drugs are dependent on protein binding is incorrect, as the effective concentrations of drugs are mainly dependent on the disposition process.¹⁸

The ED₅₀ (28.2 µg kg⁻¹) of our control group closely matched the previously reported 29,¹⁹ 30,²⁰ and 31.1 µg kg⁻¹ ²¹ ED₅₀ using the single-dose method. Similarly, the ED₉₅ of our control group (55.3 µg kg⁻¹) was comparable with the previously reported 48,¹⁹ 53,²⁰ and 57.6 µg kg⁻¹ ²² ED₉₅.

Our study has limitations, because our study design did not enable us to explore the effect of the diverse ANH conditions used in other studies that could have influenced the outcome. First, whether there is a critical threshold for ANH volume to alter the potency of cisatracurium, as we only used the recommended 15 ml kg⁻¹ volume of blood (20% of blood volume).² Second, does the type of replacement fluid make a difference: we used HES as opposed to a mixture of Ringer’s lactate and dextran in Xue and
undergo surgery with ANH. The neuromuscular blocking drug of choice in patients who do not require dosing adjustments. This would render cisatracurium as the drug of choice, as the action were not influenced by ANH, thus requiring no dose adjustments. The time-course of action of cisatracurium’s repeat dose administrations.

In conclusion, our results demonstrated that unlike other previously reported neuromuscular blocking drugs, cisatracurium dose–response relationship and time course of action were not influenced by ANH, thus requiring no dosing adjustments. This would render cisatracurium as the neuromuscular blocking drug of choice in patients who undergo surgery with ANH.

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