Comparison of the cardiovascular effects of cisatracurium and vecuronium in patients with coronary artery disease

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Purpose: Cisatracurium besylate (Nimbex® Injection, Glaxo Wellcome Inc., Research Triangle Park, NC) is an intermediate-acting bis-benzylisoquinolinium neuromuscular blocking drug that is one of the stereoisomers of atracurium. At doses ≤ 8 × ED95, it caused no clinically important cardiovascular side effects or histamine release in healthy patients. The purpose of the present study was to investigate the haemodynamic effects of high doses of cisatracurium in patients with coronary artery disease.

Methods: One hundred patients undergoing myocardial revascularization participated in a pilot study (seven patients) and a double-blinded, randomized, controlled trial comparing the haemodynamic effects of cisatracurium with vecuronium at three centres. The patients were anaesthetized using oxygen 100%, with etomidate, fentanyl and a benzodiazepine, and tracheal intubation was facilitated using succinylcholine. After baseline haemodynamic measurements, the study drug was administered over 5-10 sec according to group assignment: Group A (pilot) cisatracurium, 0.20 $mg \cdot kg^{-1}$ (4 × ED_{95}), (n = 7); Group B-cisatracurium, 0.30 $mg \cdot kg^{-1}$ (6 × ED_{95}), (n = 31); Group C-vecuronium, 0.30 $mg \cdot kg^{-1}$ (6 × ED_{95}), (n = 31); Group D cisatracurium, 0.40 $mg \cdot kg^{-1}$ (8 × ED_{95}), (n = 21); Group E-vecuronium, 0.30 $mg \cdot kg^{-1}$ (6 × ED_{95}), (n = 10). The haemodynamic measurements were repeated at 2, 5, and 10 min after cisatracurium or vecuronium.

Results: Two patients in Group D had >20% decreases in MAP, but only one required therapy for hypotension. The haemodynamic changes from pre- to post-injection in the cisatracurium patients were minimal and similar to patients receiving vecuronium.

Conclusions: In patients with coronary artery disease, rapid cisatracurium (4-8xED_{95}) boluses and vecuronium (6xED_{95}) result in minor, clinically insignificant haemodynamic side effects.

Objectif : Le bésylate de cisatracurium (Nimbex® Injection, Glaxo Wellcome Inc., Research Triangle Park, NC) est un myorelaxant di-benzylisoquinolinium à action intermédiaire qui est un des stéréo-isomères de l'atracurium. En doses de ≤ 8 × ED_{95}, il ne cause pas d'effets secondaires cardiovasculaires importants ou de libération d'histamine chez les patients en santé. L'objectif de la présente étude était d'examiner les effets hémodynamiques de fortes doses de cisatracurium chez des patients souffrant d'insuffisance coronarienne.

Méthodes : Cent patients devant subir une revascularisation myocardique ont participé à une étude pilote (sept pa tients), et à un essai contrôlé en double insu et randomisé, où ont été comparés les effets hémodynamiques du cisatracurium et du vécuronium dans trois centres. Les patients ont reçu une anesthésie avec de l'oxygène 100 %, avec étomidate, fentanyl et une benzodiazépine; on a utilisé de la succinylcholine pour faciliter l'intubation endotrachéale. Après les mesures hémodynamiques de départ, le médicament à l'étude a été administré pendant 5 à 10 secondes selon l'attribution du groupe : Groupe A (pilote) cisatracurium, 0,20 $mg \cdot kg^{-1}$ (4 × ED_{95}), (n = 7); Groupe B-cisatracurium, 0,30 $mg \cdot kg^{-1}$ (6 × ED_{95}), (n = 31); Groupe C-vécuronium, 0,30 $mg \cdot kg^{-1}$ (6 × ED95), (n = 31); Groupe D cisatracurium, 0,40 $mg \cdot kg^{-1}$ (8 × ED95), (n = 21); Groupe E- vécuronium, 0,30 $mg \cdot kg^{-1}$ (6 × ED_{95}), (n = 10). Les mesures hémodynamiques ont été reprises 2, 5 et 10 min après l'administration de cisatracurium ou de vécuronium.

Résultats : Deux patients du Groupe D ont présenté une baisse > 20 % de la TAM, mais aucune thérapie pour l'hypotension n'a été nécessaire. Les changements hémodynamiques survenus entre la préinjection et la postinjection ont été minimes et semblables chez les patients ayant reçu le cisatracurium ou le vécuronium.

Conclusion : Chez les patients souffrant d'insuffisance coronarienne, l'administration rapide de bolus de cisatracurium (4-8×ED_{95}) et de vécuronium (6×ED_{95}) n'a produit que des effets secondaires hémodynamiques mineurs, peu significatifs sur le plan clinique.

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CISATRACURIUM besylate (Nimbex® Injection, Glaxo Wellcome, Inc., Research Triangle Park, NC), is a neuromuscular blocker for which the safety, efficacy, pharmacokinetics, and pharmacodynamics have been demonstrated in ASA physical status 1 and 2 patients up to and including 8 × ED_{95} doses.[1,2] Low doses of cisatracurium (2 × ED_{95}) and vecuronium (2 × ED_{95}),[3] had minimal haemodynamic effects in patients with coronary artery disease. The present study was designed to investigate the haemodynamic effects of high doses of cisatracurium in patients with coronary artery disease.

Methods

The study was reviewed by the institutional review boards and approved at all three study centres (The Mount Sinai Medical Center, New York, NY, USA; Copenhagen University Hospital, Rigshospitalet, Denmark; and the Universitaire Ziekenhuizen, Leuven, Belgium). Patients scheduled to undergo elective coronary artery bypass graft surgery were studied in three phases that were completed consecutively:

1. an open-label pilot study of the effects of a 4 × ED_{95} dose (0.20 mg·kg^{-1}) of cisatracurium injected over 5-10 sec (Group A, n = 7),
2. a double-blinded, randomized controlled trial of a 6 × ED_{95} dose (0.30 mg·kg^{-1}) of cisatracurium (Group B, n = 31) with a 6 × ED_{95} dose (0.30 mg·kg^{-1}) of vecuronium (Group C, n = 31); and
3. a double-blinded, randomized controlled trial of an 8 × ED_{95} dose (0.40 mg·kg^{-1}) of cisatracurium (Group D, n = 21) with a 6 × ED_{95} dose (0.30 mg·kg^{-1}) of vecuronium (Group E, n = 10).

The haemodynamic data of each patient in Group A were reviewed by a safety monitor.

Groups B and C were enrolled concurrently such that at least 10 patients were enrolled per study centre. Following the preliminary analysis of the data from Groups B and C for safety, Groups D and E were enrolled concurrently. The vecuronium dose in Group E was limited to 6 × ED_{95} in order to minimize the likelihood of an adverse reaction due to inhibition of histamine N-methyl transferase.[4]

Pre-anaesthetic medication consisted of 1-4 mg lorazepam *po*. Anaesthesia was then induced using 0.05-0.30 mg·kg^{-1} etomidate, 5-19 μg·kg^{-1} fentanyl and 0.02-0.07 mg·kg^{-1} midazolam with oxygen 100% , and tracheal intubation was facilitated using 1.0-1.5 mg·kg^{-1} succinylcholine. Anaesthesia was maintained using oxygen 100%, 0.05-0.3 μg·kg^{-1}·min^{-1} fentanyl and 0.25-1.5 μg·kg^{-1}·min^{-1} midazolam. Intravenous fluid administration was limited to less than 500 ml of a crystalloid replacement solution. At least five minutes following tracheal intubation, and only if a stable haemodynamic con-

TABLE I Comparison of haemodynamics following cisatracurium, 0.30 mg·kg^{-1} (6 × ED_{95}), or Vecuronium, 0.30 mg·kg^{-1} (6 × ED_{90}) (Groups B and C) (means ± SD)

Cisatracurium (n = 30) (Group B) *Parameter*	*Baseline*	*2 Min*	*5 Min*	*10 Min*
Heart Rate (beats per min)	53 ± 10	52 ± 11*	52 ± 10*	51 ± 10*
Mean Arterial Pressure (mm Hg)	75 ± 12	75 ± 12	75 ± 13	75 ± 13
Mean Pulmonary Arterial Pressure (mm Hg)	17 ± 3	16 ± 3*	16 ± 3*	16 ± 3*
Pulmonary Capillary Wedge Pressure (mm Hg)	11 ± 3	11 ± 3	10 ± 3*	10 ± 3*
Right Atrial Pressure (mm Hg)	9 ± 3	8 ± 3*	8 ± 3*	8 ± 3*
Cardiac Index (l·min^{-1}·m^{-2})	1.82 ± 0.43	1.78 ± 0.35	1.79 ± 0.32	1.76 ± 0.30
Systemic Vascular Resistance (dyne·sec·cm^{-5})	1619 ± 378	1649 ± 401	1644 ± 371	1659 ± 364
Pulmonary Vascular Resistance (dyne·sec·cm^{-5})	152 ± 67	138 ± 57	142 ± 54	141 ± 55
Vecuronium (n = 30) (Group C) *Parameter*	*Baseline*	*2 Min*	*5 Min*	*10 Min*
Heart Rate (beats per min)	54 ± 10	55 ± 11	53 ± 10*	53 ± 10*
Mean Arterial Pressure (mm Hg)	77 ± 18	75 ± 19	75 ± 17	76 ± 18
Mean Pulmonary Arterial Pressure (mm Hg)	18 ± 5	17 ± 4*	16 ± 3*	16 ± 3*
Pulmonary Capillary Wedge Pressure (mm Hg)	11 ± 4	10 ± 3*	10 ± 3*	11 ± 3*
Right Atrial Pressure (mm Hg)	8 ± 2	7 ± 2*	7 ± 2*	7 ± 2*
Cardiac Index (l·min^{-1}·m^{-2})	1.87 ± 0.55	1.85 ± 0.53	1.87 ± 0.50	1.84 ± 0.51
Systemic Vascular Resistance (dyne·sec·cm^{-5})	1675 ± 589	1671 ± 619	1684 ± 671	1669 ± 529
Pulmonary Vascular Resistance (dyne·sec·cm^{-5})	151 ± 85	149 ± 79	137 ± 66	141 ± 62

Intragroup comparison with baseline: * $P < 0.05$

TABLE II Comparison of haemodynamics following cisatracurium, 0.40 mg·kg^{-1} (8 × ED_{95}), or Vecuronium, 0.30 mg·kg^{-1} (6 × ED_{90}) (Groups D and E) (mean ± SID)

Cisatracurium (n = 19) (Group D) *Parameter*	*Baseline*	*2 Min*	*5 Min*	*10 Min*
Heart Rate (beats per min)	56 ± 14	54 ± 13*	52 ± 11	51 ± 11*
Mean Arterial Pressure (mm Hg)	74 ± 13	71 ± 12	72 ± 12	72 ± 11
Mean Pulmonary Arterial Pressure (mm Hg)	18 ± 7	16 ± 6*	17 ± 6*	16 ± 6*
Pulmonary Capillary Wedge Pressure (mm Hg)	10 ± 5	9 ± 5	10 ± 5	10 ± 5
Right Atrial Pressure (mm Hg)	9 ± 4	8 ± 4*	8 ± 4*	8 ± 4*
Cardiac Index (l·min^{-1}·m^{-2})	2.14 ± 0.63	2.10 ± 0.66	2.15 ± 0.71	2.04 ± 0.53
Systemic Vascular Resistance (dyne·sec·cm^{-5})	1381 ± 436	1373 ± 461	1365 ± 423	1376 ± 338
Pulmonary Vascular Resistance (dyne·sec·cm^{-5})	166 ± 56	151 ± 56*	140 ± 49*	146 ± 45*
Vecuronium (n = 7) (Group E) *Parameter*	*Baseline*	*2 Min*	*5 Min*	*10 Min*
Heart Rate (beats per min)	51 ± 10	50 ± 9	49 ± 9	48 ± 8*
Mean Arterial Pressure (mm Hg)	74 ± 11	71 ± 12	72 ± 12	73 ± 11
Mean Pulmonary Arterial Pressure (mm Hg)	15 ± 4	15 ± 4	15 ± 4	15 ± 4
Pulmonary Capillary Wedge Pressure (mm Hg)	8 ± 4	8 ± 4	8 ± 4	8 ± 4
Right Atrial Pressure (mm Hg)	7 ± 4	7 ± 4	7 ± 4	7 ± 4
Cardiac Index (l·min^{-1}·m^{-2})	1.89 ± 0.29	1.85 ± 0.29	1.89 ± 0.31	1.86 ± 0.29
Systemic Vascular Resistance (dyne·sec·cm^{-5})	1535 ± 394	1505 ± 402	1496 ± 375	1552 ± 392
Pulmonary Vascular Resistance (dyne·sec·cm^{-5})	167 ± 54	156 ± 55	153 ± 59	150 ± 49

Intragroup comparison with baseline: * $P < 0.05$

dition was established (<10% change in mean arterial pressure and heart rate over five minutes), the baseline haemodynamic measurements were obtained. The haemodynamic measurements included heart rate, systolic pressure, diastolic pressure, mean arterial pressure, right atrial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, and thermodilution cardiac output. All measurements were performed in triplicate (except pulmonary capillary wedge pressure, which was performed in duplicate). Following baseline measurements, the study drug was administered as a rapid intravenous bolus into a central vein over 5-10 sec, according to group assignment. The identical haemodynamic measurements were repeated two, five, and ten minutes after drug injection.

The triplicate measurements were averaged, and these values were used to calculate stroke volume, systemic vascular resistance, and pulmonary vascular resistance. The data from the three centres were pooled. The number of haemodynamic changes ≥ 20% from the baseline values in either direction were tabulated in all groups and Fisher's Exact Test was performed to determine differences among groups. To test for statistically significant changes within Groups B, C, D, and E, ANOVA and multiple contrasts were performed. Student's t test was used to detect differences between Groups B and C, and between Groups D and E. Statistical significance was defined as a two-tailed $P < 0.05$.

Results

The review of the data from Group A yielded no safety concerns. Demographic data revealed no significant differences among groups B,C,D, and E. There were no episodes of cutaneous flushing. Two patients in Group D had decreases in mean arterial pressure exceeding 20%, but only one of these patients required therapy. Two patients (one in Group B and one in Group C) were excluded from the analysis for unstable baseline haemodynamics and protocol violations. One patient in Group E received phenylephrine for hypotension four minutes following administration of the neuromuscular blocking drug. The statistical summary of the haemodynamic data is presented in Tables I and II. Although there were multiple statistically significant haemodynamic changes from pre-injection to post-injection, in no case were the cisatracurium and vecuronium groups discordant.

Discussion

Cisatracurium is the only neuromuscular blocker that is both free of histamine-releasing properties[2] and that undergoes organ-independent Hofmann elimination.[5] The results of the present study demonstrate that haemodynamically stable patients receiving a rapidly administered bolus dose of 6-8 × ED_{95} of cisatracurium did not have haemodynamic changes that would be expected with a histamine-releasing compound. Specifically, the absence of a ≥ 20% decrease in MAP in

all but two cisatracurium patients in the study supports this conclusion. It should be noted that several patients were excluded from the haemodynamic analysis because they failed to meet the strict criteria for haemodynamic stability. Because haemodynamically unstable patients were not studied, the results of this study may not be applicable to them.

In the current study, both the cisatracurium and the vecuronium patients demonstrated small decreases in HR, MPAP, RAP and PCWP from preinjection over the 10-min postinjection period, while there was no change from preinjection for MAP. Patients undergoing anaesthesia for cardiovascular surgery are inherently unstable and do show some degree of haemodynamic variability over time in the absence of surgical stimulation. The changes seen in the current study are typical of the anaesthetized unstimulated patient, and have been seen in other studies of similar design conducted at one of the participating institutions.[6,7] For this reason, the current study included a reference group of patients receiving vecuronium, which has been shown to be devoid of haemodynamic effects in various clinical studies.[8,9] Although the maximum dose of vecuronium was limited to 6 × ED_{90} for safety reasons,[4] there is no reason to expect that this biased the results of the study.

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