Dose requirements of infusions of cisatracurium or rocuronium during hypothermic cardiopulmonary bypass

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We investigated the influence of mild hypothermic cardiopulmonary bypass (CPB) on the dose requirements of cisatracurium or rocuronium used as a continuous infusion. We studied eight patients given cisatracurium and nine given rocuronium. They were ASA class III and IV and scheduled for elective coronary artery bypass grafting. Neuromuscular transmission was monitored electromyographically. After recovery of T1/T0 to 10%, a cisatracurium infusion or a rocuronium infusion was started at a rate of 1.5 or 10 µg kg⁻¹ min⁻¹, respectively, and adjusted to maintain T1/T0 at 15%. Infusion rate and duration were recorded before, during and after CPB in each patient and the mean infusion rates were calculated. One-way ANOVA showed a statistically significant difference between the cisatracurium infusion rates before, during and after CPB: A T1/T0 of 15% could be achieved with a mean infusion rate of 1.1, 0.75 and 0.98 µg kg⁻¹ min⁻¹ before, during and after CPB, respectively. There was no significant difference between the rocuronium infusion rates before, during and after CPB. The mean rocuronium infusion rate required to maintain T1/T0 at 15% throughout the procedure was 4.1 µg kg⁻¹ min⁻¹. Cisatracurium infusion rates should be halved during CPB. Even after CPB, requirements are reduced. The same tendency occurs with rocuronium, but the changes in infusion rate were not statistically significant.

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Neuromuscular blocking drugs are commonly used during coronary artery bypass grafting (CABG). Their advantages are that they aid mechanical ventilation, decrease anaesthetic requirements, prevent patient movement and decrease oxygen consumption. Cisatracurium and rocuronium generally lack cardiovascular side-effects during high-dose opioid anaesthesia and thus have advantages for use during CABG procedures. These advantages may not, however, be observed in different clinical conditions. During CABG and, more particularly, during cardiopulmonary bypass (CPB), cisatracurium and rocuronium requirements have not been studied in detail.

Drug elimination may be reduced by relative hypoperfusion of the liver and kidney or by hypothermia during CPB. This is true for atracurium and for rocuronium. Moreover, as the clearance of cisatracurium, one of the stereoisomers of atracurium, is highly dependent on Hofmann degradation, temperature and pH changes associated with CPB are likely to affect its pharmacokinetics more than those of other neuromuscular blocking drugs. As data for the newer neuromuscular blocking drugs are scarce, cisatracurium and rocuronium infusion rates during and after CPB are adjusted empirically.

A more rational dosage regimen may reduce waste and, consequently, the cost of using these expensive new drugs. Moreover, a more predictable recovery may be important in fast tracking and minimally invasive cardiac procedures, as it may allow early extubation. Avoiding an excessively prolonged neuromuscular block may also decrease the incidence of awareness during the first hours on the intensive care unit (ICU).

Methods

After Institutional Review Board approval and written informed consent, we studied eight patients given cisatracurium followed by nine given rocuronium during CABG with mild hypothermic CPB (33°C). All patients were ASA class III and IV. Exclusion criteria were: left ventricular ejection fraction <50%; evidence of renal, hepatic, metabolic or
neuromuscular disorders; and history of medication interfering with neuromuscular transmission.

All patients were premedicated with lorazepam 2.5 mg 1 h before induction. After 3 min of preoxygenation, anaesthesia was induced with diazepam 0.15 mg kg⁻¹ and sufentanil 5 μg kg⁻¹ i.v. As soon as the eyelid reflex was absent, assisted ventilation by facemask was started with oxygen 100%. After equipotent bolus doses of cisatracurium 0.1 mg kg⁻¹ or rocuronium 0.6 mg kg⁻¹ intubation was performed as soon as the first response to the train-of-four (TOF) stimulus was present below 10%. Normocapnic ventilation was established with a Servo 900C (Siemens Elema; Stockholm, Sweden). Anaesthesia was maintained with oxygen 50% in air, propofol 1–3 mg kg⁻¹ h⁻¹ and supplemental boluses of diazepam or sufentanil. No potent inhalation anaesthetics were used. Routine monitoring included ECG, pulse oximetry, invasive arterial pressure (left radial artery) and central venous pressure (right jugular vein). Temperature was monitored at the following sites: oesophagus, rectum, skin of the forehead and the area of skin on the right arm where neuromuscular transmission monitoring electrodes had been applied.

The bypass circuit was of standard construction. Blood temperature was measured at the venous site of the bypass circuit and kept constant at 33°C during hypothermia. Rewarming to 37°C was started as soon as the surgeon had completed the last distal anastomosis. Alpha-stat pH management was used.

Neuromuscular transmission was monitored on the right arm by the EMG response of the adductor pollicis muscle to TOF stimulation of the ulnar nerve, using surface electrodes (M-NMT module; Datex-Ohmeda, Helsinki, Finland). The right arm was wrapped in a protective towel. The TOF response to a supramaximal stimulus was obtained before the initial bolus of neuromuscular blocking drug. The stimulus current range during supramaximal stimulation was 10–70 mA. The TOF was measured at 1 min intervals, using a square wave, constant current stimulus pulse with a width of 200 μs.

After recovery of T1/T0 to 10%, patients were given either cisatracurium or rocuronium, at an infusion rate of 1.5 and 10 μg kg⁻¹ min⁻¹ respectively. These dosages were based on data obtained during major non-cardiac surgery.⁸⁹ The infusion rate was adjusted to maintain T1/T0 at 15%. The concentration of the solutions used for infusion was 0.2 and 1 mg ml⁻¹ for cisatracurium and rocuronium, respectively, so that even small changes in infusion rate led to significant changes of volume delivered and, thus, to a quick alteration in effect. The infusion was discontinued just before the completion of surgery. Bolus doses of cisatracurium 0.03 mg kg⁻¹ or rocuronium 0.15 mg kg⁻¹ were given if gross movement occurred. Spontaneous recovery from neuromuscular blockade was allowed on the ICU. The results of monitoring neuromuscular transmission and all other vital parameters were displayed on a Datex AS/3 monitor and stored in a spreadsheet on a PC (Compaq).

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics in cisatracurium and rocuronium groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisatracurium group (n = 8)</td>
</tr>
<tr>
<td>Age, yr (mean (range))</td>
</tr>
<tr>
<td>Gender, male/female</td>
</tr>
<tr>
<td>Weight, kg (mean (sd))</td>
</tr>
<tr>
<td>Height, cm (mean (sd))</td>
</tr>
</tbody>
</table>

Table 2. Mean (sd) cisatracurium and rocuronium infusion rates during coronary artery bypass grafting (one-way ANOVA; significance at P<0.05)

<table>
<thead>
<tr>
<th>Infusion rate, μg kg⁻¹ min⁻¹</th>
<th>Before bypass</th>
<th>During bypass</th>
<th>After bypass</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisatracurium</td>
<td>1.10 (0.24)</td>
<td>0.75 (0.24)</td>
<td>0.98 (0.17)</td>
<td>0.01</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>4.42 (1.83)</td>
<td>3.57 (1.54)</td>
<td>4.24 (1.45)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Infusion rate and infusion duration were recorded before, during and after CPB for each patient. The mean infusion rates in both groups were derived before, during and after bypass. Statistical analysis included one-way analysis of variance (ANOVA). Significance was set at a level of P<0.05. A one-sample t-test was performed to assess if the derived mean (actual T1/T0%) was significantly different from the theoretical mean (T1/T0=15%). Results are presented as mean (sd).

Results

Anaesthesia was uneventful in all patients. No patient moved and no diaphragmatic contractions were observed. There was no need for any escape bolus dose of neuromuscular blocking drug. Patients did not sweat and their eyes did not water. They did not recall the operation. One patient in the cisatracurium group suffered from opioid-induced rigidity during induction. Although assisted ventilation was initially difficult, oxygenation was well maintained and induction was otherwise uneventful.

Table 1 shows the physical characteristics of the patients in the cisatracurium and rocuronium groups. The mean (sd) time between starting the initial infusion of cisatracurium at a rate of 1.5 μg kg⁻¹ min⁻¹ and the first adjustment to a lower dose was 34.5 (19.1) min. In the cisatracurium group, mean (sd) T1/T0 during the procedure was 14.6 (9.9)%.

This actual mean was not significantly different from the preset value (T1/T0=15%) (P=0.7). Table 2 shows the one-way ANOVA of cisatracurium infusion rates during CABG. The means differ significantly (P=0.01), with the highest rate before and the lowest during CPB.

The mean (sd) time between starting the rocuronium infusion at the initial infusion rate (10 μg kg⁻¹ min⁻¹) and the first adjustment to a lower dose was 20.2 (13.3) min. In the rocuronium group, the mean (sd) T1/T0 during the procedure was 14.2 (7.1) %; this was not significantly different from the preset value (T1/T0=15%) (P=0.2). Table 2 shows the one-way ANOVA of rocuronium infusion rates during CABG. There was no statistically significant
difference between these means (\(P=0.5\)). The mean (sd) infusion rate of rocuronium required to keep \(T1/T0\) at 15% throughout surgery was 4.1 (1.6) \(\mu\)g kg\(^{-1}\) min\(^{-1}\).

**Discussion**

During hypothermic CPB, complex changes in drug pharmacokinetics occur, prolonging the duration of action of many non-depolarizing neuromuscular blocking drugs.\(^4\) The serum concentration of neuromuscular blocking drugs may decrease when bypass is started, as a result of haemodilution,\(^10\)\(^11\) or it may increase secondary to decreased clearance and altered drug distribution.\(^12\)\(^13\)

The impairment of the metabolic function of the kidney, as a result of hypoperfusion during CPB, is expected to decrease renal elimination.\(^14\) Moreover, decreased hepatic blood flow, decreased concentration of binding proteins and decreased intrinsic activity of the liver are assumed to diminish hepatic clearance during bypass.\(^14\) These phenomena may result in a steady increase in the serum concentration of neuromuscular blocking drugs during hypothermic CPB.\(^14\) Hypothermia itself can alter the pharmacokinetics of drugs during CPB: it influences the enzymatic processes involved in drug metabolism in the liver and kidneys.\(^4\)\(^14\)

Finally, since neuromuscular blocking drugs may redistribute significantly to the lungs, they can accumulate there before bypass begins. These drugs can thus become trapped in the lungs during CPB, as circulation to the lungs during that period is restricted to the bronchial vessels. When pulmonary artery blood flow is restored during weaning from CPB, the serum concentration of these drugs may suddenly increase.\(^4\)\(^14\)

Rosen and Rosen\(^6\) concluded that pharmacokinetics during CPB depend mainly on the composition of the oxygenator, the physical properties of the drug, the use of pulsatile or non-pulsatile flow and hypothermia. Drugs with a smaller distribution volume are more affected. The oxygenator binds lipophilic drugs more avidly than those that are hydrophilic. Neuromuscular blocking drugs generally have a rather small distribution volume: cisatracurium has a slightly greater volume of distribution than atracurium,\(^15\) while rocuronium has a smaller one than vecuronium.\(^16\)

In clinical practice, serum concentrations of neuromuscular blocking drugs are not available. The degree of muscle relaxation can only be assessed by monitoring neuromuscular transmission. However, neuromuscular monitoring during hypothermia is complicated by the fact that cooling affects nerve conduction, neuromuscular transmission and muscular activity.\(^17\) The evoked response obtained in a peripheral muscle during CPB may be influenced by peripheral and core temperature gradients and alterations in skeletal muscle blood flow. Nevertheless, in the presence of hypothermia, pH disturbances and the side-effects of vasoactive drugs, neuromuscular monitoring is superior to simple clinical judgment.\(^18\)

It has been shown that, for various neuromuscular blocking drugs, the duration of action is prolonged by hypothermia.\(^10\)\(^14\)\(^19\) The half-life of cisatracurium is presumably prolonged during hypothermic CPB, as its breakdown is even more dependent on temperature and pH than that of atracurium, for which a reduced dose requirement has been observed during CPB.\(^5\) The remainder of the drug, about 15%, is cleared by the kidneys.\(^15\) The pharmacokinetics of rocuronium resemble those of vecuronium, except that the former has a smaller volume of distribution.\(^16\) The termination of the effect of rocuronium is similar to vecuronium and mainly dependent on redistribution, by hepatic uptake, followed by biliary elimination. A smaller proportion, <20%, is excreted renally.\(^20\) Smeulers and colleagues\(^6\) found that hypothermic CPB prolonged the duration of action of maintenance doses of rocuronium.

In a preliminary study,\(^21\) we concluded that a cisatracurium infusion, administered at half the initial rate (0.75 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)) during hypothermic CPB, resulted in clinically acceptable conditions. Discontinuation of the cisatracurium infusion at the start of CPB, on the contrary, led to an unacceptably high incidence of movement, suggesting that it is preferable to use a continuous infusion of neuromuscular blocking agent during CABG and CPB. In the current study, we confirmed our previous findings that a cisatracurium infusion rate of 0.75 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) was appropriate during CPB. Moreover, we found that a \(T1/T0\) of 15% could be achieved before CPB with a dose of <1.5 \(\mu\)g kg\(^{-1}\) min\(^{-1}\). Even after the bypass, cisatracurium infusion rates were lower than those before bypass, probably because of a further fall in body temperature, a tendency described in previous reports for other neuromuscular blocking drugs.\(^5\) Less rocuronium was required during and, to a lesser extent, after CPB compared with before CPB, but the differences in infusion rates were not statistically significant. In the rocuronium group, we also observed a temperature drop in the period after the bypass.

We have searched for a practical and adequate infusion regimen for the two latest commercially available neuromuscular blocking drugs, cisatracurium and rocuronium, during cardiac surgery with mild hypothermic CPB. For cisatracurium, we found that a significant reduction to half of the initial infusion rate during CPB was appropriate in clinical practice. As with atracurium, the cause is probably related to the temperature-dependent inactivation of cisatracurium. For rocuronium, a lower infusion rate was used in our study than in previous reports.\(^7\) Further reduction during CPB was not necessary. The degree of cooling during CPB may explain the discrepancy between our results and those of other investigators: while Smeulers and colleagues\(^6\) cooled patients to 25–28°C, we used only mild hypothermia (33°C).

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