Pharmacokinetics of doxacurium during normothermic and hypothermic cardiopulmonary bypass surgery

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Purpose: To compare the pharmacokinetic behaviour of doxacurium in patients undergoing normothermic or hypothermic cardiopulmonary bypass (CPB) for coronary artery bypass graft surgery.

Methods: Twenty patients in two equal groups were studied. Anaesthesia was induced with sufentanil and midazolam after a standard premedication. Doxacurium was administered at 3 × ED_{95} (80$\mu g \cdot kg^{-1}$), and anaesthesia was maintained with 0.5 $\mu g \cdot kg^{-1}$ hr^{-1} sufentanil, 0.05 $mg \cdot kg^{-1}$ midazolam and isoflurane 0.5-1% . Systemic temperature for patients in the normothermic and hypothermic groups was maintained at 33-36C and 26-30C respectively. Timed blood and urine samples were collected and pharmacokinetic parameters were estimated using a non-compartmental approach.

Results: For the normothermic and hypothermic groups, terminal elimination half-life ($t_{1/2}\beta$) was 100.1 ± 28 and 183.8 ± 60 min ($P < 0.05$) respectively, elimination half-life during the CPB phase ($T_{1/2}$ CPB) 114.5 ± 10 and 183.8 ± 60 min ($P < 0.05$), mean residence time 108.8 ± 25 and 164.8 ± 34 min ($P < 0.05$) and apparent volume of distribution at steady state 0.20 ± 0.03 and 0.26 ± 0.04 $L \cdot kg^{-1}$ ($P < 0.05$). Compared with the hypothermic group, the normothermic group had a higher rate of renal clearance (1.40 ± 0.4 *vs* 0.93 ± 0.3 $ml \cdot min^{-1} \cdot kg^{-1}$; $P < 0.05$) and a higher value for renal clearance as a percentage of the total clearance (76.2 ± 10 *vs* 58.3 ± 20%).

Conclusion: The elimination rate of doxacurium during normothermic CPB is faster than that in hypothermic CPB.

Objectif : Comparer le comportement pharmacocinétique du doxacurium chez des patients subissant une CEC normothermique ou une CEC hypothermique lors d'une chirurgie pour un pontage coronaire.

Méthodes : Vingt patients répartis en deux groupes égaux ont été étudiés. L'anesthésie a été induite avec du sufentanil et du midazolam après une prémédication standard. Le doxacurium a été administré à raison de 3 x ED_{95} (80 $\mu g \cdot kg^{-1}$), et l'anesthésie a été maintenue avec 0,5 $\mu g \cdot kg^{-1} hr^{-1}$ de sufentanil, 0,05 $mg \cdot kg^{-1}$ de midazolam et de l'isoflurane 0,5 – 1 %. La température systémique pour les patients des groupes normothermique et hypothermique a été maintenue à 33-36 °C et 26-30 °C respectivement. Les échantillons de sang et d'urine ont été prélevés à des moments déterminés et les paramètres pharmacocinétiques ont été estimés selon une approche non compartimentale.

Résultats : Pour les groupes normothermique et hypothermique, la demi-vie d'élimination finale ($t_{1/2}\beta$) était de 100,1 ± 28 et de 183,8 ± 60 min ($P < 0,05$) respectivement, la demi-vie d'élimination durant la phase de CEC ($T_{1/2}$ CEC) était de 114,5 ± 10 et de 183,8 ± 60 min ($P < 0,05$), la durée de séjour moléculaire moyenne (MRT) était de 108,8 ± 25 et de 164,8 ± 34 min ($P < 0,05$) et le volume de distribution à l'état d'équilibre était de 0,20 ± 0,03 et de 0,26 ± 0,04 $L \cdot kg^{-1}$ ($P < 0,05$). Comparé au groupe hypothermique, le groupe normothermique avait une clairance rénale à un taux plus élevé (1,40 ± 0,4 *vs* 0,93 ± 0,3 $ml \cdot min^{-1} \cdot kg^{-1}$, $P < 0,05$) et une valeur de clairance rénale plus grande en proportion de la clairance totale (76,2 ± 10 *vs* 58,3 ± 20 %).

Conclusion : Le taux d'élimination du doxacurium pendant la CEC normothermique est plus élevé que pendant la CEC hypothermique.

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HYPOTHERMIA, to reduce myocardial oxygen demand during coronary artery bypass graft surgery (CABG), has been adopted as standard practice since it was introduced by Bigelow *et al.* in 1950.[1] Cardiopulmonary bypass (CPB) is associated with haemodilution, hypotension and altered regional blood flow in addition to systemic hypothermia. These physiological changes may affect the pharmacokinetic behaviour and serum concentrations of anaesthetic drugs administered during CPB which, in turn, can affect their behaviour during cardiac surgery.[2]

McDonagh *et al.*[3] reported that the clinical duration of doxacurium is prolonged in cardiac compared with noncardiac surgery and suggested that hypothermia could be a factor. Although this study suggested hypothermia during cardiac surgery as the probable cause of the increased duration, it was made on the basis of comparisons with non-cardiac surgery. A more definite identification of the effects of hypothermia can be made by studies in which cardiac surgery is a common denominator with temperature as the variable.

Warm cardiac surgery (systemic normothermia technique), introduced by Lichtenstein *et al.*,[4] which allows for extended cross-clamp intervals,[5] has been suggested as an alternative to hypothermic CPB. Normothermic CPB has been reported to reduce the incidence of ventricular fibrillation on reperfusion and also to eliminate the need for rewarming prior to weaning from CPB.

This trial was designed to study the pharmacokinetic behaviour of doxacurium during hypothermic and normothermic CPB in patients undergoing CABG surgery. The results of such a study should provide unequivocal answers without the confounding effects that enter in comparisons of cardiac with noncardiac surgery.

Methods

The study was undertaken after Institutional Ethics Committee approval and informed consent. Twenty patients undergoing elective CABG surgery were randomized into normothermic (n = 10) or hypothermic (n = 10) CPB groups. Patients with evidence of clinical renal or hepatic impairment were excluded. No patient was known to be taking medication or to have diseases related to neuromuscular transmission.

All subjects received routine ß-adrenoceptor blocking drugs and nitrates for the control of angina pectoris till the time of surgery. Premedication consisted of 0.15 $mg \cdot kg^{-1}$ diazepam *po* two hours before surgery, 0.15 $mg \cdot kg^{-1}$ morphine and 0.07 $mg \cdot kg^{-1}$ perphenazine *im*. Anaesthesia was induced with 3 $\mu g \cdot kg^{-1}$ sufentanil and 0.07 $mg \cdot kg^{-1}$ midazolam. Doxacurium was administered at 3 x ED_{95} ($80 \mu g \cdot kg^{-1}$) and the trachea was intubated three minutes later. A nerve stimulator was used to deliver square-wave impulses of 0.2 msec duration in a train-of-four (TOF) sequence (2 Hz for two seconds) via needle electrodes adjacent to the left ulnar nerve at the wrist and set to repeat every three minutes after tracheal intubation. The left arm and hand were extended at 70 and were covered with a blanket to prevent heat loss. Controlled ventilation was adjusted to maintain the $P_{ET}CO_2$ at 35-45 mmHg. Anaesthesia was maintained with 0.5 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ sufentanil, 0.05 $mg \cdot kg^{-1}$ midazolam, nitrous oxide 67% in oxygen and isoflurane (0.5-1%). In instances where there were clinical signs of recovery from doxacurium (such as diaphragmatic movement or when the first twitch was >10% of the baseline), additional muscle relaxation was achieved with pancuronium so as not to interfere with doxacurium assay.

Cardiac surgery and CPB

Standard CABG surgery was performed. Heparin (300 $IU \cdot kg^{-1}$) was administered as a bolus prior to CPB. The ascending aorta was cannulated and CPB was instituted using two caval cannulae. A membrane oxygenator (Maxima or Bard) and nonpulsatile pump were used. A non-blood prime was used (2 L Ringers lactate, 25 g albumin, 50 mEq sodium bicarbonate, 25 g mannitol and 5,000 u heparin). The aorta was cross-clamped and cardiac arrest was facilitated with an infusion of 1000 ml cold crystalloid cardioplegia (4-8C) into the aortic root (infusion rate of 300 $ml \cdot min^{-1}$). After the initial arrest, subsequent infusions of blood cardioplegia (400 ml at 8 - 12C) were repeated every 15 min or sooner if electrical activity resumed. Blood cardioplegia consisting of 1 mg nitroglycerin, 530 mg citrate phosphate dextrose, 20 mEq potassium chloride and 360 $mg \cdot L^{-1}$ tromethamine was infused after distal anastomosis was completed. Haematocrit was maintained at 20-25%. During CPB, pump flow rates were 2.0-2.5 $l \cdot min^{-1} \cdot m^{-2}$ and mean arterial pressure was maintained at 50-60 mmHg with nitroprusside or neosynephrine titration. A single cross-clamp was used for the proximal and distal anastomoses during coronary bypass. Prior to the removal of the aortic cross-clamp, an infusion of 300 ml warm blood containing 12.5 g mannitol was given through the aortic root. Cardiopulmonary bypass was terminated when patients were haemodynamically stable. Upon termination of extracorporeal circulation, the effects of heparin were reversed with protamine sulphate.

Patients randomized to the normothermic and

hypothermic groups had their systemic temperatures maintained at 33-36C and 26-30C respectively. All patients were actively rewarmed to 38C prior to removal of the aortic cross-clamp and weaning from the CPB.

Blood sampling and doxacurium assay, pharmacokinetic analysis

Blood samples for determination of plasma concentration of doxacurium were drawn from the arterial line catheter at 0, 2, 5 and 10 min post-doxacurium, five minutes pre-CPB and at 5, 10, 15, 30, 45, 60, 90 and 120 min during CPB. Urine was collected from an indwelling urinary catheter during surgery till completion of surgery to determine the total volume for estimation of renal excretion and clearance of doxacurium. Urine samples and centrifuged plasma were stored at -70C until high pressure liquid chromatography (HPLC) analysis. Blood samples were also collected preop and postop for estimation of plasma creatinine level for the two groups.

Plasma and urinary concentrations of doxacurium were measured by a specific HPLC assay, as previously described.[6,7] Solid-phase extraction cartridges (Prep Sep C18, Fisher Scientific, Fair Lawn, NJ) were conditioned after which plasma and the internal standard, tubocurarine, were added to the cartridge. After several washings, the analytes were eluted from the bonded phase with a mixture of 80:20 methanol and 0.05 M monobasic ammonium phosphate (pH 3). The chromatographic separation was performed on a 5 μ Spherisorb C_1 column (125 mm). The HPLC mobile phase was a 30:69:1 v/v mixture of 0.05 M monobasic ammonium phosphate (pH 3), acetonitrile and methanol. *d*-tubocurarine was detected at 280 nm and doxacurium at 210 nm by a programmable wavelength ultraviolet detector. The method used was accurate (mean, 98.3%; coefficient of variation, 4.8%), sensitive (lower limit of quantification, 4 $ng \cdot ml^{-1}$) and reproducible (mean coefficient of variation, 6.9%); it was linear for plasma concentration in the low range (up to 62.5 $ng \cdot ml^{-1}$, $r^2 = 0.9999$).

Using a non-compartmental approach, the following parameters were derived using standard formulae:[8] terminal elimination half-life ($t_{1/2}ß$), mean residence time (MRT), total body clearance (CL) and apparent volume of distribution at steady state (Vdss). Elimination half-life was also determined during the CPB phase ($T_{1/2}$ CPB) by log-linear regression analysis of the terminal portion of doxacurium plasma concentration time curve (at least five data points).

Renal clearance was calculated for the 10 to 60 min period post-CPB by dividing the amount of doxacurium excreted in urine by the area under the plasma concentration-time curve for the same period. The fraction of the total body clearance that is renal (% Cl renal/CL) and the percentage of doxacurium excreted unchanged into the urine during the period of the study (% Xu Total) were also determined.

Comparisons between the normothermic and the hypothermic groups were made using Student's t test and analysis of variance; a $P < 0.05$ was considered significant. All results were expressed as mean ± standard deviation (SD).

Results

No differences in preoperative or intraoperative characteristics were found between the two experimental groups (Table I). Patients in the normothermic group took a shorter time for reperfusion than those in the hypothermic group. There was no difference between the two groups in terms of the prime volume for CPB (Table II). Three and two patients in the normothermic and hypothermic groups respectively received pancuronium at a dose of 0.05 $mg \cdot kg^{-1}$ post-CPB for clinical signs of recovery from the neuromuscular blockade of doxacurium.

Doxacurium plasma concentration-time profile (Figure 1) showed a biexponential decline. All pharmacokinetic parameters, $t_{1/2}ß$, $T_{1/2}$ CPB, MRT and Vdss, showed differences ($P < 0.05$; Table III), values in all cases being lower for the normothermic than for the hypothermic group. The difference between the

TABLE I. Demographic data for patients in the normothermic and hypothermic groups.

	Normothermic (n = 10)	*Hypothermic (n = 10)*
Age (yr)	68.0 ± 6.6	64.6 ± 6.0
Sex (Male: Female)	9 : 1	8 : 2
Weight (kg)	73.0 ± 13.9	73.8 ± 12.7
Height (cm)	168.6 ± 8.6	170.5 ± 10.5

TABLE II Cardiopulmonary data

	Normothermic	Hypothermic
Duration of CPB (min)	89.7 ± 16	102.8 ± 36
Duration of cross-clamp time (min)	59.8 ± 7	69.3 ± 25
Duration of re-perfusion (min)	16.5 ± 6*	29.9 ± 8
Prime Volume (ml)	2200.0 ± 75	2255.0 ± 72
Added Blood/Fluid (ml)	1272.2 ± 419	1370.0 ± 681
Total Fluid Used in CPB (ml)	2803.5 ± 508	3038.0 ± 672
Cardioplegic Volume (ml)	489.5 ± 120	625.0 ± 211

* $P < 0.05$

TABLE III Pharmacokinetic parameters of doxacurium during normothermic and hypothermic CPB

	Normothermic (n = 10)	*Hypothermic (n = 10)*
$t_{1/2}$ ß (min)	100.1 ± 28.2*	144.2 ± 29.8
$T_{1/2}$ CPB (min)	114.5 ± 9.9*	183.8 ± 59.9
MRT (min)	108.8 ± 24.8*	164.8 ± 39.3
Vdss (L·kg–1)	0.20 ± 0.03*	0.26 ± 0.04

* $P < 0.05$

TABLE IV Clearance of doxacurium during normothermic and hypothermic CPB.

	Normothermic (n = 8)	Hypothermic (n = 8)
CL (ml·min^{-1}·kg–1)	2.0 ± 0.5	1.6 ± 0.2
Cl renal (ml·min^{-1})	102 ± 26*	66 ± 21
Cl renal (ml·min^{-1}·kg^{-1})	1.40 ± 0.4*	0.93 ± 0.3
% Cl renal/ CL	76.2 ± 10$	58.3 ± 20
% Xu Total	28.5 ± 13	24.2 ± 10

* $P < 0.05$
$ $P = 0.07$

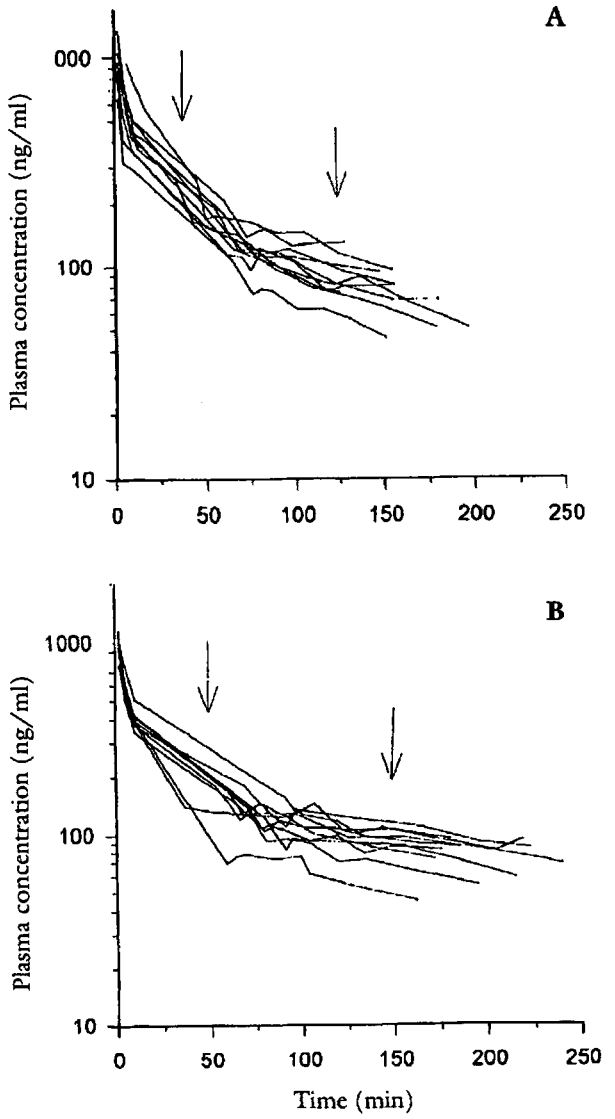

FIGURE 1 Pharmacokinetic profiles of doxacurium in normothermic (A) and hypothermic (B) CPB over time after an intravenous bolus dose of 80 µg·kg–1 *iv* for patients undergoing CABG surgery. The arrows indicate the range for the beginning and end of CPB.

two groups was 30.6% for $t_{1/2}$ß, 37.7% for $T_{1/2}$ CPB, 33.9% for MRT and 23.1% for Vdss.

The results of the clearance analysis are shown in Table IV. The preop and postop plasma creatinine levels were comparable for the two groups. Total body clearance of doxacurium tended to be higher in normothermic than in hypothermic subjects (2.0 *vs* 1.6 ml·min^{-1}·kg^{-1}; $P = 0.09$). Renal clearance was higher in the normothermic (1.4 ml·min^{-1}·kg^{-1}) than in the hypothermic group (0.93 ml·min^{-1}·kg^{-1}), and renal clearance as a percentage of the total clearance was 76.2% and 58.3% respectively ($P = 0.07$). The mean percentage of the dose excreted unchanged in the urine was 28.5% in 82 min of urine collection for the normothermic group, and 24.2% in 107 min of urine collection in the hypothermic group.

Discussion

In discussing the results, the pharmacokinetics for the normothermic group will be treated as the experimental group and the hypothermic as the control since hypothermic CPB is the common practice. The major finding is that all pharmacokinetic parameters for doxacurium are reduced in normothermic CPB compared with hypothermic CPB. The $t_{1/2}$ß was 30.6% shorter for normothermic than for hypothermic and this was associated with a higher renal clearance rate for normothermic CPB. The $t_{1/2}$ß is influenced by changes in volume of distribution, clearance or both.[9] The value of $t_{1/2}$ß for the normothermic group (100.1 ± 28 min) is comparable to that reported in populations of a similar age in noncardiac surgical procedures (96 - 120 min with isoflurane 0.5-0.8%)[6,10] indicating that changes secondary to hypothermia were the cause for the prolonged elimination half- life for the hypothermic CPB group. Similarly, the prolongation in the $t_{1/2}$ß for muscle relaxants[11] and for opioids such as fentanyl[9] reported during hypothermic CPB may also be due to hypothermia. Our study further showed that the elimination $T_{1/2}$ of doxacurium during the CPB phase was

decreased by 37.7% in the normothermic compared with that in the hypothermic group. Prolonged elimination time may be expected to have an effect on the medication requirements. However, Kavanagh *et al.*[12] reported, on clinical grounds, that there was no difference in the anaesthetic medication requirements between patients receiving warm or cold CPB.

The values of $t_{1/2}ß$ and $T_{1/2}$ CPB differed because the regression was not carried using the same data points. The average duration of CPB was 90-100 min, therefore one to three samples were taken after cessation of CPB. For each patient, the slope of the plasma concentration-time curve is consistently slower during the CPB period (Figure 1). The authors felt that the post-CPB data points should be included as well in the estimation of the $t_{1/2}ß$, to minimise the error associated with a short sampling time. This decision was based upon the fact that no disruption in the plasma concentration-time curve was observed upon cessation of CPB. The Vdss (0.20 ± 0.03 $L \cdot kg^{-1}$) obtained in our study for the normothermic group is comparable to the value reported for doxacurium in elderly populations undergoing non-cardiac surgery.[6,10] There was a 23.1 % decrease in Vdss in the normo thermic compared to the hypothermic group.

The Vdss is known to be influenced by the initial fluid volume status, intraoperative blood loss and fluid replacement.[2] In this study, all these variables were similar for the two groups. It has been suggested that protein binding is decreased by hypothermic CPB[2] which points to this as a possible factor in the Vdss difference found in our study. Further, it has been reported that the reduced metabolic requirement induced by hypothermia results in shunting of blood away from vital organs to the muscles.[13] This increase in vasodilatation in the skeletal muscles may also account for the difference in Vdss.

Renal clearance of doxacurium is nearly 50% higher for the normothermic group compared to the hypothermic CPB group. Hypothermia appears to have an effect analogous to that of hypotension on renal function in animals.[2] Renal tubular enzymes involved in active secretion or reabsorption may exhibit temperature-dependent activity[13] and the depression in enzyme activity induced by hypothermia may diminish metabolic clearance of certain drugs. Another factor may be the decrease in blood flow to the kidneys induced by increasing renal vascular resistance caused by hypothermia.[14] The total clearance in the two groups did not differ (2.0 and 1.6 $ml \cdot min^{-1} \cdot kg^{-1}$ for the normothermic and hypothermic groups respectively) and our values agree with those reported Dresner *et al.*[10] (2.5 $ml \cdot min^{-1} \cdot kg^{-1}$) and Gariepy *et al.*[6] (1.7 $ml \cdot min^{-1} \cdot kg^{-1}$).

Although the disposition of doxacurium in humans has not been fully characterised, preliminary studies indicate that it is excreted by both urinary and biliary pathways.[10,15,16] In our study, renal clearance as a percentage of total clearance was 76.2% and 58.3% for the normothermic and hypothermic groups respectively ($P = 0.07$). This would indicate that a higher proportion of the drug excreted is by the hepatobiliary pathway in hypothermia, although in terms of the quantity excreted by this pathway the two groups may not differ. These results demonstrate that there are important differences in the disposition of doxacurium between hypothermic and normothermic CPB.

This is the first study to compare the pharamacokinetic behaviour of an anaesthetic agent during warm and cold heart surgery. Agreement of our pharmacokinetic parameter estimates for the normothermic group with those for noncardiac surgery would indicate that CPB *per se* does not change the pharmacokinetic behaviour of doxacurium but that it is hypothermia that leads to these kinetic changes. Further studies may be needed to evaluate the other anaesthetic agents being currently used for normothermic CPB.

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