Vecuronium pharmacokinetics and pharmacodynamics during hypothermic cardiopulmonary bypass in infants and children

Davinia Withington B M FRCA MRCP,
Guillaume Menard B Pharm,†
Jennifer Harris MD FRCPC,
Pradeep Kulkarni MD FRCA,
François Donati MD PhD FRCPC,‡
France Varin PhD†

Purpose: To determine the effect of moderate and deep hypothermic cardiopulmonary bypass (CPB) on the pharmacokinetic and pharmacodynamic behaviour of vecuronium in infants and children.

Methods: We studied 12 patients undergoing surgery for congenital heart disease under narcotic-nitrous oxide anesthesia. Neuromuscular blockade was maintained constant (T1 4-10% by Datex electromyograph) by adjusting a vecuronium infusion. Plasma vecuronium concentrations (Cpss) were analysed by HPLC to describe a pseudosteady-state during each of the pre-CPB, CPB and post-CPB phases. Paired arterial blood samples were taken 20 min apart after at least 20 min of constant infusion.

Results: Nine cases were analysed, mean age 20 mo, mean weight 9 kg. Three patients had deep and six moderate hypothermia. In the pre-CPB phase Cpss fell into two groups (mean ± SD: 330 ± 42 ng·ml^{-1}; 127 ± 27 ng·ml^{-1}, $P <$ 0.001); similarly the clearances showed a bimodal distribution (mean ± SD: 5.08 ± 0.94; 11.51 ± 0.2 ml·min^{-1}·kg^{-1} $P <$ 0.001), although in different patients. During CPB this bimodal distribution disappeared. Vecuronium infusion rate (VIR) decreased by 84% and 92% from pre-CPB to CPB phase in deep and moderate hypothermia groups respectively ($P <$ 0.05), paralleled by decreases in Cpss of 36% ($P >$ 0.05) and 52% ($P <$ 0.05).

Conclusion: Changes in vecuronium requirements and plasma concentrations during CPB demonstrate that vecuronium pharmacokinetics and pharmacodynamics are both affected by hypothermic CPB in infants. The finding of bimodal distributions for plasma vecuronium and vecuronium clearance highlights the need for individual monitoring of neuromuscular blockade in this age group.

Objectif : Déterminer l'effet d'une circulation extracorporelle (CEC) avec hypothermie modérée ou profonde sur les paramètres pharmacocinétiques et pharmacodynamiques du vécuronium chez des nourrissons et des enfants.

Méthode : Nous avons étudié 12 patients opérés pour cardiopathie congénitale sous anesthésie avec un mélange de narcotique et de protoxyde d'azote. Le blocage neuromusculaire a été maintenu constant (T1 4-10 % avec un électromyographe Datex) en ajustant une perfusion de vécuronium. Les concentrations plasmatiques de vécuronium (Cpss) ont été analysées par chromatographie liquide haute performance (CLHP) afin de définir l'état pseudo-équilibre pendant chacune des étapes pré-CEC, CEC et post-CEC. Des échantillons appariés de sang artériel ont été prélevés à intervalles de 20 min, après au moins 20 min de perfusion constante.

Résultats : Neuf cas ont été analysés, âgés de 20 ms et pesant 9 kg en moyenne. Trois patients avaient une hypothermie profonde et six, une modérée. Pendant la pré-CEC, les Cpss se séparent en deux groupes (moyenne ± écart type : 330 ± 42 ng·ml^{-1}; 127 ± 27 ng·ml^{-1}, $P <$ 0,001); les clairances ont affiché une distribution bimodale (moyenne ± écart type : 5,08 ± 0,94; 11,51 ± 0,2 ml·min^{-1}·kg^{-1} $P <$ 0,001), chez différents patients cependant. Pendant la CEC, cette distribution bimodale a disparu. La vitesse de perfusion du vécuronium (VPR) a diminué de 84 % et 92 %, comparée à celle de la pré-CEC chez les patients avec hypothermie profonde et modérée, respectivement ($P <$ 0,05), parallèlement à une baisse des Cpss de 36 % ($P >$ 0,05) et de **52 % ($P <$ 0,05)**.

Conclusion : Les besoins différents de vécuronium et les changements de concentrations plasmatiques pendant la CEC montrent que la pharmacocinétique et la pharmacodynamie du vécuronium sont influencées par une CEC hypothermique chez l'enfant. La découverte de distributions bimodales de vécuronium plasmatique et de clairance du vécuronium, souligne la nécessité d'un monitorage du blocage neuromusculaire chez les patients de cet âge.

STUDIES performed both in animals and humans during hypothermic CPB have indicated that hypothermia below 32°C increases sensitivity to vecuronium,[1–5] pancuronium,[1,4,6] atracurium,[5,7–9] rocuronium,[10–12] metocurine[13] and doxacurium[14] but not to alcuronium[15,16] or d-tubocurarine.[1,17] Some studies have examined pharmacodynamic parameters only[1,4,5,7,18] but other authors have performed a complete pharmacokinetic-pharmacodynamic study.[10,12,13] It has also been shown that neuromuscular transmission decreases during hypothermia, even in the absence of muscle relaxants.[19]

The effect of hypothermic CPB on neuromuscular blockade (NMB) pharmacokinetics, pharmacodynamics or pharmacokinetic-pharmacodynamic interactions has not been studied in neonates or children. Many pediatric cardiac surgery cases are performed under deeper hypothermia than in adults[20] and deep hypothermic circulatory arrest is frequently used in infants < 10 kg undergoing complex congenital heart repairs. This procedure enables the study of the effects of deep hypothermia on NMB.

This study uses a constant neuromuscular blockade method to examine the effect of hypothermia on vecuronium pharmacokinetics and pharmacodynamics during cardiopulmonary bypass (CPB) in neonates and infants with the aim of establishing appropriate dosing schedules. Although the lungs of the subjects in this study will remain ventilated postoperatively, many children having simpler cardiac procedures may be extubated in the operating room or within a few hours of surgery, thus making this an issue of clinical as well as scientific relevance.

Methods
Clinical Protocol
After Institutional Review Board approval and with parental written informed consent, 12 patients (ASA physical status 1 or 2) participated in this study. All were undergoing corrective surgery for congenital cardiac anomalies. Patients with neuromuscular, pulmonary, hepatic or renal disease were excluded. Other exclusion criteria were history of multiple allergies or the concurrent administration of drugs known to or suspected to interfere with neuromuscular function.

In the Operating Room, after instituting routine monitoring (pulse oximeter, non-invasive blood pressure, electrocardiogram) anesthesia was induced with 5-10 μg·kg⁻¹ fentanyl and 1-2 mg·kg⁻¹ ketamine, or by inhalational induction with halothane in those babies in whom intravenous access was difficult. Ketamine increments, 1 mg·kg⁻¹, were used as necessary to prevent movement while the Datex Relaxograph™ was applied. Anesthesia was maintained with fentanyl or sufentanil and midazolam infusions, inhalational agents being avoided to prevent potentiation of NMB. Temperatures (nasopharyngeal (NP), rectal and skin) were recorded throughout the procedure along with vecuronium infusion rate (IR), pH and hematocrit. Central venous access was by internal jugular cannulation and arterial cannulation was via the radial artery. Intravenous fluid (Ringers' lactate) was given at maintenance rate before CPB.

Cardiopulmonary bypass was conducted with non-pulsatile flow and membrane oxygenation. The pump was primed with blood, albumin 25% and Normosol R to maintain hematocrit between 0.18 and 0.28. Heparin (300 U·kg⁻¹) was administered to achieve an activated coagulation time of 480 sec. Cardioplegia solution was Plegisol (St. Thomas' Hospital solution) given at 30 ml·kg⁻¹ after aortic cross-clamping.

Pharmacodynamics: neuromuscular monitoring
The Datex Relaxograph delivers stimuli every 20 sec to measure an integrated electromyogram (EMG) and gives digital readouts of first twitch ratio (T1%) and train-of-four ratio (TOFR). The former, the ratio between first twitch and the baseline first twitch response, was used for controlling NMB by changes in vecuronium infusion rate. Electrode positions were adjusted to obtain good responses at the adductor hallucis brevis muscle. The foot was used for monitoring to leave both hands free in case of failed radial artery cannulation on one side.

After baseline T1% response had been obtained, blood was taken for baseline vecuronium assay[15] and muscle relaxation was initiated with 0.1 mg·kg⁻¹ vecuronium, given by peripheral *iv*, and the tracheal was intubated at 90% depression of T1%. Once the T1% had returned to 5% of baseline an infusion was started at 0.075 mg·kg⁻¹ via the central venous line and adjusted to maintain a T1% of 5 to 10%. This technique, the maintenance of a constant degree of blockade by adjustment of infusion rate, is well described in the literature on NMB dose-response relationships.[5,7,8] If the twitch response declined to zero, the infusion was stopped until a twitch returned.

Pharmacokinetics
The establishment of "pseudo-equilibrium" during each of the pre-CPB, CPB and post-CPB phases was verified by paired blood samples; once the infusion rate had been constant for at least 20 min the first of a pair of blood samples was drawn, the second sample being taken 20 min later. Each sample was of 3 ml taken into heparinised tubes kept on ice. When the difference in

plasma concentration for the two specimens was < 15%, the mean value was used for pharmacokinetic analysis. For larger differences, the concentration of the last sample drawn was used for analysis.

Total body clearance was determined by dividing the infusion rate by the plasma concentration at pseudo-equilibrium (Cpss).

Assay
Determination of vecuronium concentration in plasma was carried out by high performance liquid chromatography with electrochemical detection.[21] The mobile phase consisted of 0.033 M phosphoric acid (60% v/v) and acetonitrile (40% v/v) adjusted to a final pH of 5.55 with ammonium hydroxide. A prepacked Spherisorb CN (5 μm, particle size) was used for HPLC separation at 35°C. Solid-phase extraction of vecuronium from plasma was performed using Bond-Elut C1 cartridges.

Although the assay was previously validated for plasma concentrations of vecuronium ranging from 3.9 to 4000 ng·ml^{-1}, calibration curves ranging from 15 to 500 ng·ml^{-1} were used for this study. The assay is specific for vecuronium and its metabolites but the latter were not quantified. The coefficient of variation for the intra-assay precision is less than 10%. The inter-assay reproducibility gave a mean coefficient of variation of 5.8% for vecuronium.

Statistical analysis
Values are expressed as means and standard deviations. The F-test has been used to establish comparability in variance between groups. Student's t test was used to assess statistical significance at a 5% level of significance between hypothermic and deep hypothermic groups. Paired t testing was used to assess statistical significance at a 5% level of significance between pre-CPB, during CPB and post-CPB values.

Results
Of the 12 patients enrolled, two were excluded because of complete neuromuscular blockade throughout surgery and one for technical difficulties. The nine patients analysed (five male, four female) had a mean age of 20 mo and a mean weight of 9 kg (Table I). Three of these patients underwent DHCA (one male and two female). Hematocrit was 0.31-0.43 pre-CPB and 0.18-0.28 during CPB (Table II). Prime volume was 800-1250 ml. The T1% was maintained at 3-11% throughout anesthesia. In some cases the T1% declined to zero until the infusion rate was reduced adequately. Samples were taken when the infusion rate had been constant for at least 20 min, with T1% in the

target range. Infusion rates, vecuronium plasma concentrations (Cpss) and plasma clearance (Cl) before, during and after CPB are represented for each subject in Figure 1.

At each stage of the operation (pre-CPB, CPB and post-CPB), no statistical differences were observed for IR, Cpss and Cl between the moderate and deep hypothermia groups and the values were therefore pooled together. During CPB, the infusion rate declined by 84% (from 0.074 ± 0.025 mg·kg^{-1}·hr^{-1} to 0.012 ± 0.016 mg·kg^{-1}·hr^{-1}) for patients who underwent deep hypothermia and by 92% (from 0.099 ± 0.067 mg·kg^{-1}·hr^{-1} to 0.008 ± 0.014 mg·kg^{-1}·hr^{-1}) for patients under moderate hypothermia. In the moderate hypothermia group, there were differences for I.R. ($P = 0.021$) and Cpss ($P = 0.032$). In the deep hypothermia group, the difference was statistically significant for the I.R. only ($P = 0.019$) when comparing pre-CPB with CPB values. During the pre-CPB period, at a mean temperature of 35.8°C, a wide range of infusion rates was used to maintain adequate muscle relaxation. A bimodal distribution was observed with respect to pre-CPB vecuronium pseudosteady-state Cpss associated with a 3-11 T1% (Figure 1). Patients appeared equally divided into two clear groups requiring higher (330 ± 42 ng·ml^{-1}) or lower (127 ± 27 ng·ml^{-1}) vecuronium Cpss ($P < 0.001$) for adequate NMB.

The mean clearance for the pooled data was 7.22 ml·min^{-1}·kg^{-1}. Upon visual inspection of individual data (Figure 1), patients also appeared to fall into two distinct groups having a mean Cl of 5.08 ± 0.94 (3.82;6.17) or 11.51 ± 0.2 ml·min^{-1}·kg^{-1}, respectively ($P < 0.001$). Patients in the two groups did not differ

TABLE I Demographic data

Patients	Age (mo)	Weight (kg)	Sex	Type of surgery
B	10	7.3	F	TOF
C	41	19.5	F	Fontan
D	66	17.7	M	ASD, VSD, PDA
G	8	7	M	RVOTO, ASD, BTS
H	32	9.7	M	Repair of truncus
T	11	7.12	M	TOF
L (DHCA)	0.5	2	F	Switch
N (DHCA)	6	6.2	M	Glenn shunt
O (DHCA)	4	4.8	F	TOF

Legend
TOF:	Tetralogy of Fallot repair
ASD:	atrial septal defect closure
VSD:	ventricular septal defect closure
BTS:	Blalock Taussig shunt
PDA:	patent ductus arteriosus ligation
RVOTO:	relief of right ventricular outflow tract obstruction
CAVC:	complete atrioventricular canal repair

TABLE II Intraoperative data

Patients	CPB (min)	XC (min)	DHCA (min)	Lowest Temp (NP)	pre Hct	CPB Hct	Prime vol (ml)
B	135	73		26.4	0.35	0.21	600
C	141	72		17.2	0.38	0.18	1000
D	63	38		28.5	0.32	0.18	1250
G	67	26		29	0.38	0.26	600
H	285	169		20	0.42	0.28	600
T	166	73		21.8	0.42	0.23	600
L (DHCA)	169	95	48	18.9	0.43	0.25	325
N (DHCA)	183	82	29	19.8	0.31	0.24	600
O (DHCA)	136	70	52	19.4	0.43	0.28	450

in terms of demographics, type of lesion (cyanotic *vs* non-cyanotic) or type and parameters of surgery. However, patients having a lower Cl were not necessarily those requiring higher vecuronium Cpss.

During CPB, infusion rates were reduced (from 0.091 ± 0.056 mg·kg^{-1}·hr^{-1} to 0.009 ± 0.014 mg·kg^{-1}·hr^{-1}) compared with the pre-CPB period ($P = 0.002$) and a narrow range of infusion rates was required to maintain adequate relaxation in all patients. The bimodal distribution of vecuronium Cpss persisted with mean values of 146 ± 25 ng·ml^{-1} and 90 ± 24 ng·ml^{-1} for the higher and lower groups, respectively ($P = 0.01$). However, vecuronium Cl appeared evenly distributed in these patients.

In the post-CPB period, although infusion rate requirements were not different from those in the pre-CPB period (0.034 ± 0.033 mg·kg^{-1}·hr^{-1} *vs* 0.091 ± 0.056 mg·kg^{-1}·hr^{-1}; $P = 0.087$), Cpss levels remained slightly lower than those observed in the pre-CPB period (138 ± 47 ng·ml^{-1} *vs* 217 ± 112 ng·ml^{-1}; $P = 0.008$). The pre-post difference is mostly attributable to the group of patients who had required higher vecuronium levels in the pre-CPB period (330 ± 42 ng·ml^{-1} *vs* 156 ± 41 ng·ml^{-1}; $P = 0.0016$). Overall, Cl in the post-CPB period did not differ from that observed pre-CPB; some patients having either lower or higher Cl compared with the pre-CPB period. However, a bimodal distribution was not observed for either the Cpss or Cl.

Discussion

This study demonstrates a major effect of hypothermia on vecuronium pharmacokinetics and pharmacodynamics in neonates and infants undergoing CPB. It also provides an indication of the variability of vecuronium clearance in pediatric patients undergoing major cardiovascular surgery.

Age has previously been shown to affect neuromuscular blocker requirement.[22] Although information on pediatric dose adjustment for vecuronium is scarce, it has been reported that neonates and infants have the lowest vecuronium requirements,[23] children between three and ten years have the highest,[24] while adolescents and adults require an almost identical dose to infants.[25] Onset is faster in infants, while duration, recovery times and rate of recovery after neostigmine reversal are longest in infants and shortest in children.[26] These differences highlight why it is inappropriate to extrapolate adult data to the pediatric age range.

In view of the wide spread of ages in our study population, age and weight-related changes in vecuronium clearance were also expected. The longer duration and recovery time for infants receiving vecuronium have previously been attributed to a slower clearance or a larger volume of distribution (Vd).[26,27] However, despite the important role played by the liver in the biliary excretion of vecuronium, Fisher *et al.* have shown that there were no age-related differences in Cl, thus the longer mean residence time in infants results from a larger Vd.[28] Extracellular fluid (ECF) decreases from 44% of body weight at birth to 26% at one year. Therefore, because vecuronium distributes into ECF, its Vd would be expected to be greater in infants than in older subjects. Similar age-related changes in steady state Vd have been demonstrated for d-tubocurarine,[26,29] another drug whose Vd is similar to that of ECF. Neuromuscular function recovers mainly during the distribution phase of vecuronium rather than in the elimination phase.[28]

In the pre-CPB phase, we unexpectedly found a group of vecuronium responsive and a group of vecuronium resistant children, as defined by lower and higher pseudosteady-state Cpss respectively while T1 was 3-11%. This bimodal distribution is of interest with respect to safety. The fact that some patients (not definable by age, weight or pathophysiology) require a higher than average vecuronium dose to achieve a target T1% underlines the importance of individual
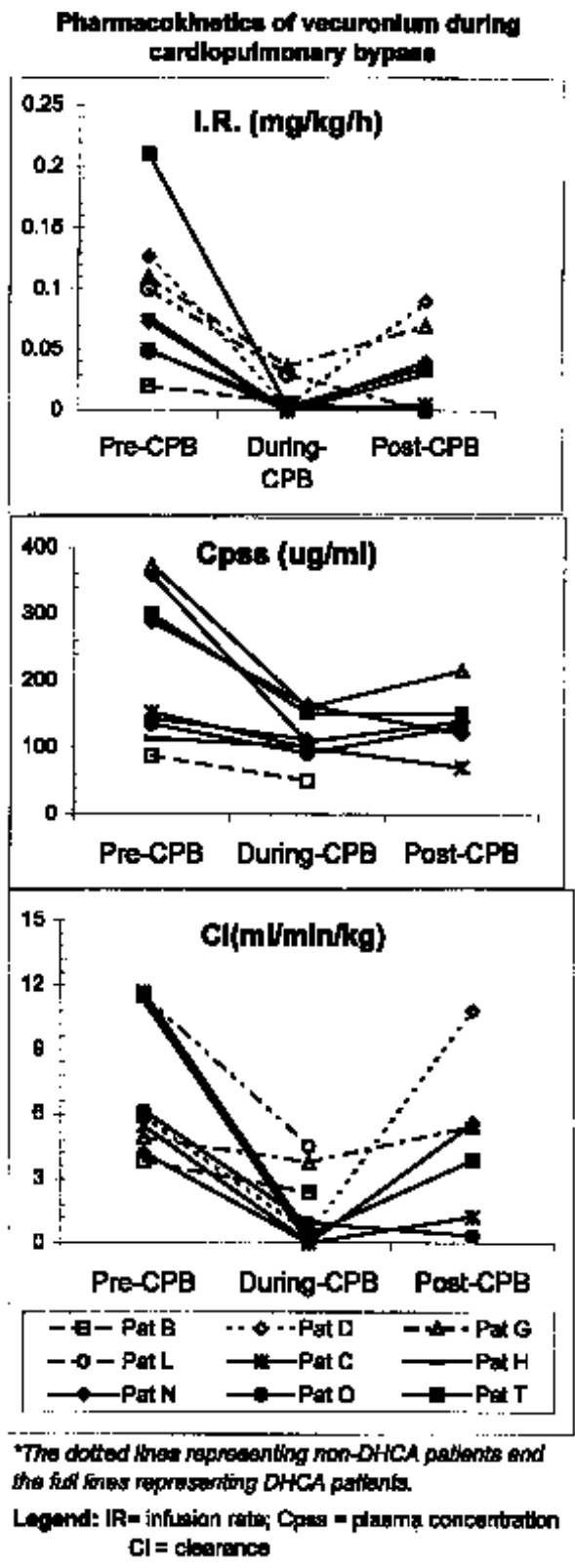
Pharmacokinetics of vecuronium during cardiopulmonary bypass

I.R. (mg/kg/h)

Cpss (ug/ml)

Cl(ml/min/kg)

Legend:
- — 🔲 — Pat B
- — ⬦ — Pat D
- — ▲ — Pat G
- — ⭘ — Pat L
- — ✳ — Pat C
- —— Pat H
- — ◆ — Pat N
- — ● — Pat O
- — ■ — Pat T

*The dotted lines representing non-DHCA patients and the full lines representing DHCA patients.

Legend: IR = infusion rate; Cpss = plasma concentration
Cl = clearance

FIGURE Pharmacokinetics of vecuronium during cardiopulmonary bypass.

neuromuscular monitoring during anesthesia. The maintenance of adequate NMB during cardiac surgery is essential, not only to prevent movement during delicate surgery, but to prevent rises in oxygen consumption which may occur in poorly paralysed patients. However, during CPB the plasma vecuronium concentrations in these two groups became indistinguishable although there was a greater decrease in the resistant group during CPB compared to pre-CPB values. This cluster may be explained by an almost complete block caused by hypothermia rather than increased sensitivity to the NMB, meaning that during hypothermia the patient's initial sensitivity to vecuronium is no longer determinant.

A bimodal distribution was also found for pre-CPB clearance. The group having a lower Cl had values comparable to those observed in adult patients (mean range of 4.00–5.29 ml·min·kg^{-1}).[18,30,31] Although a clear explanation cannot be provided for this finding, our wide age range and the well known bell-shaped of the age-related change in Cl for NMB[32] contributes to the already identified difficulty in adjusting dose requirements in pediatrics. However, during the CPB period, the gap disappeared between these two groups. One might deduce that the initial condition of the patient and their general hemodynamic function are mostly responsible for the pre-post difference in Cl.

Many pharmacokinetic factors are altered by CPB.[33] Hemodilution is responsible for an increase in the apparent Vd and in the free fraction of drugs, while changes in hemodynamics will directly alter hepatic and renal clearances. The impact of hemodilution is mostly apparent on initiation of CPB, as reflected by an increase in muscle relaxant requirement.[34,35] Such an increase was not observed in our patients the samples having been collected after the IR has been constant for at least 20 min at the lowest temperature. Since the median pump priming volume was 600 ml (Table II), the increase in Vd would have been large in the 2 kg patient, but around 20% in the bigger patients if one assumes a Vd of at least 0.2 L·kg^{-1} (the extracellular fluid volume) i.e., weight-related. We did not find changes in IR and Cpss to be weight-related. The 30 – 48% reduction in hepatic blood flow resulting from CPB will, in turn, cause a lower biliary excretion of vecuronium and necessitate a decrease in the infusion rate to maintain a suitable degree of muscle relaxation.[36–38]

In addition to these physiological changes, hypothermia may also affect muscle relaxation by further altering vecuronium distribution/excretion pattern and by reducing acetylcholine release and/or muscle contractility.[39] During hypothermic CPB,

vecuronium ceases to be a short-acting muscle relaxant and behaves like pancuronium.[4,5] Animal work has suggested that a likely explanation for this is a partial failure of acetyl choline release[40] which has been suggested in man by Feldman's work.[41] Decreased muscle perfusion during hypothermia may also decrease dissociation of non-depolarising neuromuscular blocker from the receptor, thus prolonging its action.[42] In adults, mild to moderate hypothermia has been demonstrated to prolong the action of, and recovery from, vecuronium and pancuronium and thus increase the patient's sensitivity to muscle relaxant.[1,4,5] Twitch tension is unaffected by temperatures above 35.2°C but decreases by approximately 15% per degree Celsius decrease in muscle temperature below this value. However, core hypothermia must be distinguished from muscle hypothermia.[43] During CPB, core temperature should provide a close approximation of muscle temperature. It is possible that, although core and skin temperatures returned to normal values post CPB, muscle temperature may have remained low, thereby explaining the lower IR and Cpss values. Unfortunately, muscle temperature was not monitored in our children due to the ethical concern about using needle electrodes.

The net effect of combined CPB and hypothermia is not readily foreseeable. In our study, vecuronium requirements were decreased during CPB but pseudosteady-state Cpss were decreased in the moderate hypothermia group but not significantly decreased in the deep hypothermia group. This may be due to the small number of patients in the deep hypothermia group. A similar finding has previously been reported for pancuronium in adult patients undergoing moderate hypothermia (28.3 ± 0.4°C).[44] In our patients the mean reduction in vecuronium requirements during CPB for deep and moderate hypothermia groups were respectively 84% less and 92% less than the control rate at 36°C. In three of five patients vecuronium infusion had to be stopped, probably as a consequence of hypothermia. A similar trend was observed for vecuronium by Kansanaho *et al.* in adults patients under moderate and deep hypothermia.[34] During the post-CPB period, rewarming returned the infusion requirements towards pre-CPB values in most patients.

Impaired renal and hepatic function resulting from CPB-related hemodynamic changes are postoperative complications that may affect drug plasma clearance.[39,45,46] Due to our small sample size and the apparent bimodal distribution observed in our patients during the pre-CPB period, it was impossible to identify a general trend in the relative changes in Cl during the post-CPB period.

In conclusion, our results demonstrate that the pharmacokinetic and pharmacodynamic behaviour of vecuronium are changed during and after hypothermic CPB in children. The major findings are a 84 to 92% decrease in vecuronium requirement during CPB in the deep and moderate hypothermic group, respectively. The infusion rate reduction was associated with a lesser decrease in pseudo steady-state plasma concentration in infants undergoing moderate hypothermic CPB. In almost 70%, vecuronium plasma clearance was found to be similar to that reported in adults. Finally, variations in vecuronium requirements, plasma concentration and clearance could not be correlated with age in our small patient sample.

References
1 *Buzello W, Schluermann D, Pollmaecher T, Spillner G* Unequal effects of cardiopulmonary bypass-induced hypothermia on neuromuscular blockade from constant infusion of alcuronium, d-tubocurarine, pancuronium, and vecuronium. Anesthesiology 1987; 66: 842–6.

2 *Eriksson LI, Viby-Mogensen J, Lennmarken C* The effect of peripheral hypothermia on a vecuronium-induced neuromuscular block. Acta Anaesthesiol Scand 1991; 35: 387–92.

3 *Heier T, Caldwell JE, Sessler DI, Miller RD.* Mild intra-operative hypothermia increases duration of action and spontaneous recovery of vecuronium blockade during nitrous oxide-isoflurane anesthesia in humans. Anesthesiology 1991; 74: 815–9.

4 *Buzello W, Schluermann D, Schindler M, Spillner G* Hypothermic cardiopulmonary bypass and neuromuscular blockade by pancuronium and vecuronium. Anesthesiology 1985; 62: 201–4.

5 *Denny NM, Kneeshaw JD* Vecuronium and atracurium infusions during hypothermic cardiopulmonary bypass. Anaesthesia 1986; 41: 919–22.

6 *d'Hollander AA, Duvaldestin P, Henzel, D, Nevelsteen M, Bomblet JP.* Variations in pancuronium requirement, plasma concentration, and urinary excretion induced by cardiopulmonary bypass with hypothermia. Anesthesiology 1983; 58: 505–9.

7 *Flynn PJ, Hughes R., Walton B.* Use of atracurium in cardiac surgery involvng cardiopulmonary bypass with

induced hypothermia. Br J Anaesth 1984; 56: 967–71.

8   *Flynn PJ, Hughes R., Walton B, Jothilingam S.* Use of atracurium infusions for general surgical procedures including cardiac surgery with induced hypothermia. Br J Anaesth 1983; 55: 135S–8.

9   *Leslie K, Sessler DI, Bjorksten AR, Moayeri A.* Mild hypothermia alters propofol pharmacokinetics and increases the duration of action of atracurium. Anesth Analg 1995; 80: 1007–14.

10 *Smeulers NJ, Wierda JMKH, van den Broek L, Gallandat Huet RCG, Hennis PJ.* Hypothermic cardiopulmonary bypass influences the concentration-response relationship and the biodisposition of rocuronium. Eur J Anaesthesiol 1995; 12(Suppl11): 91–4.

11 *Beaufort AM, Wierda JMKH, Belopavlovic M, Nederveen PJ, Kleef UW, Agoston S.* The influence of hypothermia (surface cooling) on the time-course of action and on the pharmacokinetics of rocuronium in humans. Eur J Anaesthesiol 1995; 12(Suppl11: 95–106.

12 *Smeulers NJ, Wierda JMKH, van den Broek L, Gallandat Huet RCG, Hennis PJ.* Effects of hypothermic cardiopulmonary bypass on the pharmacodynamics and pharmacokinetics of rocuronium. J Cardiothorac Vasc Anesth 1995; 9: 700–5.

13 *Avram MJ, Shanks CA, Henthorn TK, Ronai AK, Kinser J, Wilkinson CJ.* Metocurine kinetics in patients undergoing operations requiring cardiopulmonary bypass. Clin Pharmacol Ther 1987; 42: 576–81.

14 *McDonagh P, Dupuis J-Y, Curren M, Kitts J, Wynands JE.* Pharmacodynamics of doxacurium during cardiac surgery with hypothermic cardiopulmonary bypass. Can J Anaesth 1996; 43: 134–40.

15 *Meakin G, Shaw EA, Baker RD, Morris P.* Comparison of atracurium-induced neuromuscular blockade in neonates, infants and children. Br J Anaesth 1988; 60: 171–5.

16 *Sorooshian SS, Stafford MA, Eastwood NB, Boyd AH, Hull CJ, Wright PMC* Pharmacokinetics and pharmacodynamics of cisatracurium in young and elderly adult patients. Anesthesiology 1996; 84: 1083–91.

17 *Walker JS, Shanks CA, Brown KF.* Altered *d*-tubocurarine disposition during cardiopulmonary bypass surgery. Clin Pharmacol Ther 1984; 35: 686–94.

18 *Shanks CA, Avram MJ, Fragen RJ, O'Hara DA.* Pharmacokinetics and pharmacodynamics of vecuronium administered by bolus and infusion during halothane or balanced anesthesia. Clin Pharmacol Ther 1987; 42: 459–64.

19 *Buzello W, Pollmaecher T, Schluermann D, Urbanyi B.* The influence of hypothermic cardiopulmonary bypass on neuromuscular transmission in the absence of muscle relaxants. Anesthesiology 1986; 64: 279–81.

20 *Rebeyka I.* Hypothermia. *In*: Jonas RA, Elliott MJ (Eds.). Cardiopulmonary Bypass in Neonates, Infants and Young Children. Oxford: Butterworth Heinemann Ltd., 1994: 54–66.

21 *Ducharme J, Varin F, Bevan DR, Donati F, Théorêt Y.* High-performance liquid chromatography-electrochemical detection of vecuronium and its metabolites in human plasma. J Chromatogr 1992; 573: 79–86.

22 *Meretoja OA.* Neuromuscular blocking agents in paediatric patients: influence of age on the response. Anaesth Intensive Care 1990; 18: 440–8.

23 *Meretoja OA.* Is vecuronium a long-acting neuromuscular blocking agent in neonates and infants? Br J Anaesth 1989; 62: 184–7.

24 *Meistelman C, Agoston S, Kersten UW, Saint-Maurice C, Bencini AF, Loose J-P.* Pharmacokinetics and pharmacodynamics of vecuronium and pancuronium in anesthetized children. Anesth Analg 1986; 65: 1319–23.

25 *Meretoja OA* Vecuronium infusion requirements in pediatric patients during fentanyl- N_2O-O_2 anesthesia. Anesth Analg 1989; 68: 20–4.

26 *Fisher DM, Miller RD.* Neuromuscular effects of vecuronium (ORG NC45) in infants and children during N_2O, halothane anesthesia. Anesthesiology 1983; 58: 519–23.

27 *Gibaldi M, Levy G, Hayton W.* Kinetics of the elimination and neuromuscular blocking effect of d-tubocurarine in man. Anesthesiology 1972; 36: 213–8.

28 *Fisher DM, Castagnoli K, Miller RD.* Vecuronium kinetics and dynamics in anesthetized infants and children. Clin Pharmacol Ther 1985; 37: 402–6.

29 *Fisher DM, O'Keeffe C, Stanski DR, Cronnelly R, Miller RD, Gregory GA.* Pharmacokinetics and pharmacodynamics of d-tubocurarine in infants, children, and adults. Anesthesiology 1982; 57: 203–8.

30 *Sohn YJ, Bencini AF, Scaf AHJ, Kersten UW, Agoston S.* Comparative pharmacokinetics and dynamics of vecuronium and pancuronium in anesthetized patients. Anesth Analg 1986; 65: 233–9.

31 *Lynam DP, Cronnelly R, Castagnoli KP, Canfell PC, Caldwell J, Arden J, Miller RD.* The pharmacodynamics and pharmacokinetics of vecuronium in patients anesthetized with isoflurane with normal renal function or with renal failure. Anesthesiology 1988; 69: 227–31.

32 *Meretoja OA, Wirtavuori K, Neuvonen PJ.* Age-dependence of the dose-response curve of vecuronium in pediatric patients during balanced anesthesia. Anesth Analg 1988; 67: 21–6.

33 *Rosen DA, Rosen KR.* Elimination of drugs and toxins during cardiopulmonary bypass. J Cardiothorac Vasc Anesth 1997; 11: 337–40.

34 *Kansanaho M, Hynynen M, Olkkola KT.* Model-driven closed-loop feedback infusion of atracurium and vecuronium during hypothermic cardiopulmonary bypass. J Cardiothorac Vasc Anesth 1997; 11: 58–61.

35 *Searle NR, Thomson I, Dupont C, et al.* A two-center study evaluating the hemodynamic and pharmacodynamic effects of cisatracurium and vecuronium in patients undergoing coronary artery bypass surgery. J Cardiothorac Vasc Anesth 1999; 13: 20–5.

36 *Koska AJ III, Romagnoli A, Kramer WG.* Effect of cardiopulmonary bypass on fentanyl distribution and elimination. Clin Pharmacol Ther 1981; 29: 100–5.

37 *Mathie RT.* Hepatic blood flow during cardiopulmonary bypass. Crit Care Med 1993; 21: S72–6.

38 *Koizumi M, Matsumoto N, Ueda K.* Influences of cardiopulmonary bypass and fentanyl anesthesia on hepatic circulation and oxygen metabolism in beagles. Anesth Analg 1998; 86: 1177–82.

39 *Rosow C, Eckhardt WF.* The pharmacology of cardiopulmonary bypass. Seminars in Anesthesia 1991; 10: 122–8.

40 *Thornton RJ, Blakeney C, Feldman SA.* Proceedings. The effect of hypothermia on neuromuscular conduction. Br J Anaesth 1976; 48: 264.

41 *Feldman SA* Hypothermia and neuromuscular blockade (Letter). Anesthesiology 1979; 51: 369–71.

42 *Feldman SA.* Muscle Relaxants, 2nd ed, Vol 1. In the series: Major Problems in Anesthesia. Philadelphia: W.B. Saunders Company, 1979: 137–52.

43 *Heier T, Caldwell JE, Sessler DI, Miller RD.* The effect of local surface and central cooling on adductor pollicis twitch tension during nitrous oxide/ isoflurane and nitrous oxide/ fentanyl anesthesia in humans. Anesthesiology 1990; 2: 807–11.

44 *d'Hollander AA, Duvaldestin P, Henzel D, Nevelsteen M, Bomblet JP.* Variations in pancuronium requirement, plasma concentration, and urinary excretion induced by cardiopulmonary bypass with hypothermia. Anesthesiology 1983; 58: 505–9.

45 *Buylaert WA, Herregods LL, Mortier EP, Bogaer MG* Cardioplumonary bypass and the pharmacokinetics of drugs. Clin Pharmacokinet 1989; 17: 10–26.

46 *Taylor CA.* Surgical hypothermia. Pharmacol Ther 1988; 38: 169–200.