

Variations in Pancuronium Requirement, Plasma Concentration, and Urinary Excretion Induced by Cardiopulmonary Bypass with Hypothermia

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To determine the effects of cardiopulmonary bypass (CPB) and hypothermia on the neuromuscular blockade produced by pancuronium, this relaxant was infused intravenously into 10 anesthetized patients to produce and maintain 90% depression of the twitch tension of the adductor pollicis muscle following supramaximal ulnar nerve stimulation. Infusion rates, plasma concentration of pancuronium, and adductor pollicis temperature were measured every 15 min. During the normothermic period preceding the start of CPB, the pancuronium requirement, the pancuronium plasma concentration, and muscle temperature were (mean \pm SEM): $238 \pm 12 \mu\text{g} \cdot \text{m}^{-2} \cdot 15 \text{ min}^{-1}$, $0.31 \pm 0.01 \mu\text{g/ml}$, and $33.9 \pm 0.1^\circ \text{C}$, respectively. At the beginning of CPB, the pancuronium infusion rate increased to $362 \pm 32 \mu\text{g} \cdot \text{m}^{-2} \cdot 15 \text{ min}^{-1}$ ($P < 0.001$) despite a decrease in the muscle temperature to $29.2 \pm 0.9^\circ \text{C}$ ($P < 0.001$) and in pancuronium plasma concentration to $0.22 \pm 0.02 \mu\text{g/ml}$. During sustained muscle hypothermia to $28.3 \pm 0.4^\circ \text{C}$ the pancuronium plasma concentration remained constant at $0.22 \pm 0.01 \mu\text{g/ml}$ ($P < 0.001$) while the requirement decreased to $94 \pm 15 \mu\text{g} \cdot \text{m}^{-2} \cdot 15 \text{ min}^{-1}$ ($P < 0.001$). After the muscle temperature was returned to $34 \pm 0.6^\circ \text{C}$, the plasma pancuronium concentration and requirements increased to $0.35 \pm 0.05 \mu\text{g/ml}$ and $392 \pm 32 \mu\text{g} \cdot \text{m}^{-2} \cdot 15 \text{ min}^{-1}$ ($P < 0.001$), respectively. After CPB, these values were $0.39 \pm 0.04 \mu\text{g/ml}$ and $239 \pm 25 \mu\text{g} \cdot \text{m}^{-2} \cdot 15 \text{ min}^{-1}$. These results demonstrate that pancuronium requirements are increased at the beginning of CPB because of circulatory volume changes and again during rewarming of the patient once muscle temperature reaches about 34°C . (Key words: Anesthesia: cardiovascular. Hypothermia. Neuromuscular relaxants: pancuronium.)

EXTRACORPEAL CIRCULATION may be accompanied by important variations in the degree of curarization.¹ At least two factors appear to be of importance: 1) variations in the plasma concentration of the curarizing agent secondary to the expansion of the circulatory volume at the onset of extracorporeal circulation; and 2) changes in the pharmacokinetic and pharmacodynamic properties of nondepolarizing neuromuscular blocking

agents caused by variations in body temperature²⁻⁴ during cardiopulmonary bypass (CPB).

The available data do not distinguish the respective contributions of hemodilution and hypothermia to changes in neuromuscular-blocking effects. We therefore have undertaken a quantitative evaluation of the requirements for pancuronium during extracorporeal circulation with hypothermia using the on-demand infusion method⁵ to maintain a stable predetermined level of twitch height. In addition, we measured the changes in plasma concentration and urinary excretion of pancuronium.

Methods

This study was approved by the Brussels University Ethical Committee on Human Investigation. Ten consenting adult patients [age, body weight and height (mean \pm SEM): 51 ± 8 yr, 75 ± 10 kg, 169 ± 7 cm, respectively] undergoing aorto-coronary bypass grafting procedures were studied. Preoperative cardiac catheterization demonstrated normal cardiac output (dye dilution) and left ventricle ejection fraction greater than 45% (cineangiography) in all patients. The patients continued to take betablockers, nitrate derivatives, and benzodiazepines during the preoperative period. A standard preoperative dose of diazepam (0.2 mg/kg) was administered orally 45 min before transfer to the operating room. Anesthesia was induced with intravenous flunitrazepam (0.03 mg/kg) and fentanyl (0.005 mg/kg) while $\text{O}_2/\text{N}_2\text{O}$ 50/50 was administered by face mask. Once anesthesia was deemed adequate, the ulnar nerve was stimulated at the cubital fossa (thin-walled, 25-gauge needles) using a Grass® 88 nerve stimulator at a frequency of 0.1 Hz with supramaximal impulses of 0.2-ms duration. The response of the adductor pollicis was measured via a force displacement transducer (UC3; UL4-20, Statham®) and recorded on a polygraph. When a consistent control tension was achieved, a bolus injection of pancuronium (0.07 mg/kg) was administered which decreased the twitch height value to 5–10% of the control value. After tracheal intubation, the patients were ventilated mechanically to maintain PaCO_2 [checked by repeated arterial blood-gas analysis, (Coring® 175)] between 37 and 42 mmHg corrected for rectal temperature. The twitch height level thereafter

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TABLE 1. Pancuronium Requirement, Plasma Concentration, and Adductor Pollicis Temperature

	Period I before CPB (n = 38)	Period II CPB Start and Cooling (n = 10)	Period III CPB before Rewarming (n = 37)	Period IV CPB after Rewarming (n = 11)	Period V after CPB (n = 32)
Pancuronium requirement ($\mu\text{g} \cdot \text{m}^{-2} \cdot 15 \text{ min}^{-1}$)	239 \pm 12* (185–303)	362 \pm 32 (189–541)‡	94 \pm 15 (40–181)‡	392 \pm 32 (239–607)‡	239 \pm 25 (133–366) NS
Pancuronium plasma concentration ($\mu\text{g}/\text{ml}$)	0.31 \pm 0.01 (0.13–0.42)	0.22 \pm 0.02 (0.14–0.48) NS	0.22 \pm 0.01 (0.14–0.48)†	0.35 \pm 0.05 (0.15–0.75) NS	0.39 \pm 0.04 (0.16–0.80) NS
Muscle temperature ($^{\circ}\text{C}$)	33.9 \pm .1 (32.5–35.4)	29.2 \pm 0.9 (24.3–32.5)‡	28.3 \pm 0.4 (24.3–32.5)‡	34.0 \pm 0.6 (30.6–32.5) NS	33.9 \pm 0.3 (31.1–37.3) NS

* Mean \pm SEM, (range), n = number of measurements pooled in a period.

† $P < 0.01$; ‡ $P < 0.001$; NS = not significant.

Bilateral Bonferroni t test unpaired. Each period is compared with Period I.

was maintained constant at $10 \pm 3\%$ of its initial value by manually adjusting the flow of a Harvard® syringe containing 80 $\mu\text{g}/\text{ml}$ of pancuronium in saline.

The pancuronium requirements were calculated every 15 min by measuring the displacement of the piston during each period. Anesthesia was maintained with 50% nitrous oxide, fentanyl, dehydrobenzperidol, and flunitrazepam as reported previously.⁶

During cardiopulmonary bypass, a disposable bubble oxygenator (OPTIFLO® II) was used in all cases: the priming solution consisted of 1.5 l of gelatin polymer (HAEMACCEL®) and 0.3 g/kg mannitol given as a 20% solution. Moderate hypothermia (24° – 26° C rectal) and subsequent rewarming of the patient were produced with the passive thermal exchanger of the oxygenator connected to an active hydraulic cooling-warming system (GAMBRO®, hyper-hypothermia unit, HYP 10-200) and was supplemented by a water mattress.

The arterial pump of the CPB machine continuously maintained the perfusion flow above $2.2 \text{ l} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$. During CPB, the arterial plasma K^{+} was measured repeatedly (ORION® Space Stat 30 sodium-potassium analyzer) and maintained within physiologic limits by adding small boluses of potassium chloride, the total amount being about 0.8–1.0 mEq/kg. Total pancuronium plasma and urinary concentrations were determined by a spectrofluorimetric method⁷ in arterial blood and urine sampled every 15 min. This method, accurate to 0.02 $\mu\text{g}/\text{ml}$ in our laboratory, does not distinguish pancuronium from its metabolites.

Urinary creatinine was measured by automated analysis (Technicon®) using the reaction of Jaffe. Arterial blood samples also were used to determine the hematocrit by micromethod and the blood protein content by Biuret reaction (Technicon). The temperature of the stimulated muscle was monitored by needle electro-

thermometer (no. 524 Yellow Spring Instruments) and recorded at the time of pancuronium plasma sampling.

The data were analyzed by performing variance analysis, unpaired bilateral Bonferroni t test, and Spearman correlation test. According to the number of interperiods comparisons done, the data were considered significant when P values were less than 0.01.

Results

The results of the different determinations performed at 15-min intervals were pooled into five periods corresponding to: Period I, measurements performed 60 min after pancuronium bolus administration and before the start of cardiopulmonary bypass; Period II, data obtained during active cooling within the first 15 min of CPB; Period III, results observed before the patient's rewarming; Period IV, observations collected during CPB once the muscle temperature was returned to above 32.5° C; and period V, measurements obtained after CPB. During Period I, the pancuronium requirement was (mean \pm SEM): $238 \pm 12 \mu\text{g} \cdot \text{m}^{-2} \cdot 15 \text{ min}^{-1}$ (table 1). During Period II, the demand for muscle relaxant increased significantly, while in Period III, the pancuronium dosage requirement decreased significantly. Once the patients were rewarmed (Period IV) the patient's pancuronium demand again increased significantly. After CPB (Period V) the pancuronium requirement returned to the prebypass level. The pancuronium plasma concentrations were decreased significantly during Periods II and III, while they were increased significantly during Periods IV and V. The muscle temperature differed from the prebypass value only during Periods II and III. The sequential hematocrit values measured during the five periods were 45 ± 0.2 , 29 ± 0.1 , 30 ± 0.1 , 32 ± 0.1 , and $34 \pm 0.1\%$; all the values observed during and after CPB were sig-

TABLE 2. Urinary Pancuronium and Creatinine Excretion Observed before, during, and after CPB Session

	Period I before CPB	Period II Start of CPB	Period III CPB before Rewarming	Period IV CPB after Rewarming	Period V after CPB
Diuresis (ml)	21 ± 4*	66 ± 25†	80 ± 18‡	50 ± 12 NS	34 ± 4 NS
Pancuronium urinary excretion ($\mu\text{g} \cdot \text{m}^{-2} \cdot 15 \text{ min}^{-1}$)	172 ± 68	156 ± 64 NS	238 ± 88 NS	64 ± 17 NS	64 ± 11 NS
Creatinine plasma clearance (ml/min)	121 ± 18	146 ± 21 NS	90 ± 24 NS	51 ± 16†	62 ± 6†

* Mean ± SEM, (range), n = number of measurements pooled in a period.

† $P < 0.01$; ‡ $P < 0.001$; NS = not significant.

nificantly different ($P < 0.001$) from the initial one. The same pattern was observed for the serum proteins measured concomitantly: 7.02 ± 0.14 , 4.8 ± 0.08 , 5.1 ± 0.09 , and 5.4 ± 0.11 g/dl.

The urinary excretion of pancuronium was determined every 15 min in five patients. The results are shown in table 2. For interperiods comparisons, final statistical analysis (Bonferroni t test) shows that the variations of renal pancuronium excretion observed never

gained the significant level, while the endogenous creatinine clearance was decreased significantly during Periods IV and V. Using pooled data, the pancuronium excreted in the urine was significantly correlated with creatinine clearance: $R = 0.62$ ($P < 0.01$) and with diuresis: $R = 0.54$ ($P < 0.01$) (Spearman correlation test). Finally, the ratios between the cumulative pancuronium infused and that excreted in the urine ranged from 0.06 to 0.39 (fig. 1).

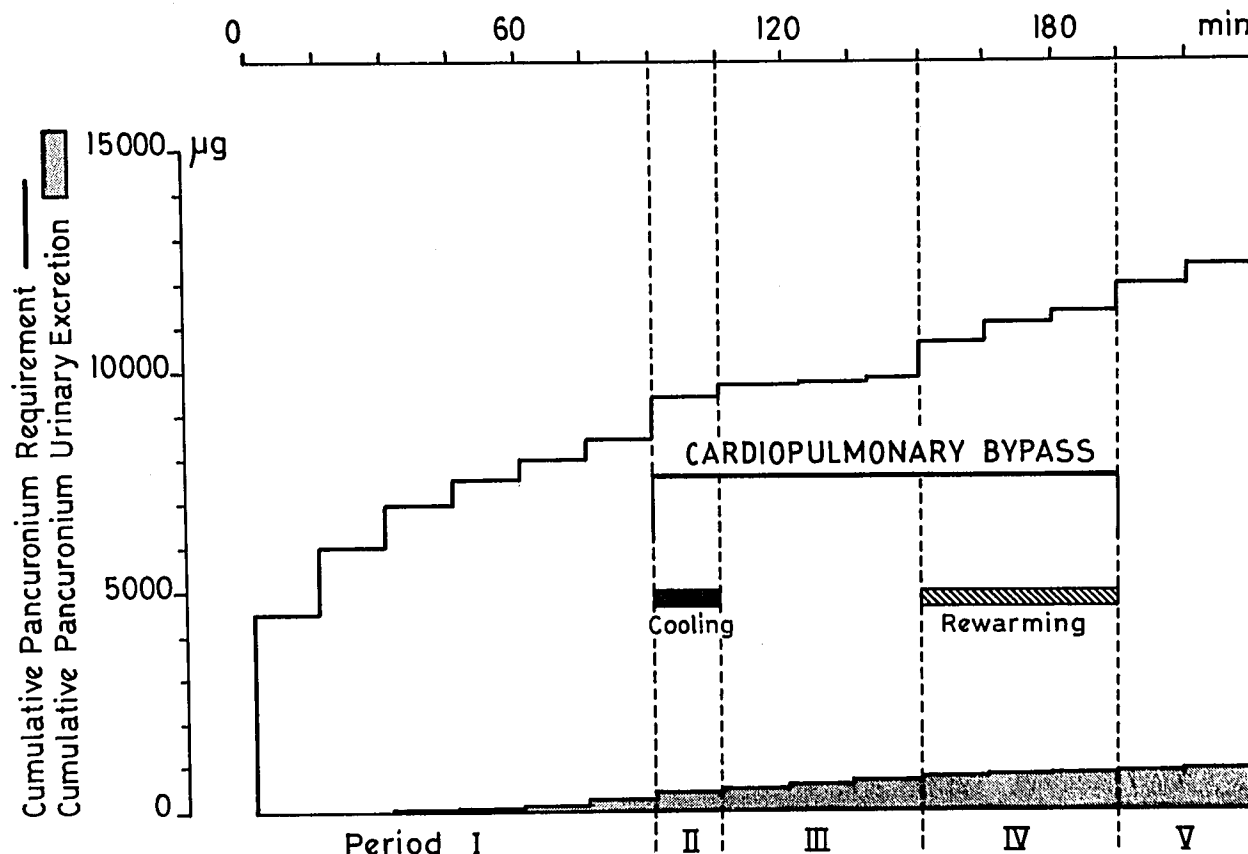


FIG. 1. Illustration from a single patient of the cumulative changes of the pancuronium administered and excreted in the urine.

Discussion

As reported previously,⁵ pancuronium requirements stabilize within 45–60 min of starting a demand infusion. Subsequently, during extracorporeal circulation, pancuronium requirements are influenced principally by the following factors: change in muscle temperature, variation in the circulatory volume at the beginning of cardiopulmonary bypass, and total body hypothermia which reduces the rate of pancuronium plasma clearance.³ We have observed that when muscle temperature decreases to 28–29° C, plasma pancuronium concentration decreases from 0.31 to 0.22 $\mu\text{g}/\text{ml}$. This is consistent with the results of Miller *et al.* who compared the plasma concentrations of pancuronium necessary to maintain a given degree of paralysis, evaluated by recording mechanical activity, in the normo- and hypothermic cat.³ In our patients, the mean pancuronium requirement during normothermia was $239 \mu\text{g} \cdot \text{m}^{-2} \cdot 15 \text{ min}^{-1}$ and decreased to $94 \mu\text{g} \cdot \text{m}^{-2} \cdot 15 \text{ min}^{-1}$ during the stabilized hypothermia of Period III. This decrease of nearly 60% in pancuronium consumption while muscle temperature is maintained in the range of 29° C is of the same order of magnitude as that observed by Miller and Roderick in the cat.² The importance of muscle temperature in the functioning of the neuromuscular junction is also evident in the rewarming phase (Period IV). Here, both pancuronium requirement and plasma concentration increased.

The increase in plasma concentration at the end of and after extracorporeal circulation as compared with prebypass values could be due to the accumulation of pancuronium metabolites—3 mono, 17 mono, 3–17 di OH pancuronium—in the circulation. These metabolites are measured together with the unchanged molecule by the spectrofluorimetric method but are less active at the neuromuscular junction.⁸ Thus, their presence could account wholly or in part for the increased plasma concentration necessary to maintain twitch height at 10% of its initial value.

Initiation of cardiopulmonary bypass results in a substantial increase in circulatory volume and, thus, in the pancuronium distribution volume. This explains the observed increase in pancuronium requirement at the beginning of Period II despite the fact that pancuronium plasma concentration already has reached its lowest value. CPB associated hemodilution also provokes an important decrease in plasma protein concentration and thus increases the free fraction of circulating pancuronium. Increased free pancuronium may reduce slightly the augmentation in pancuronium requirement due to hemodilution itself. This phenomenon is limited in the case of pancuronium where plasma protein binding is of the order of 30%, but could significantly limit the

effects of hemodilution in the case of *d*-tubocurarine and fazadinium, *i.e.*, where about 50% of the drug is protein bound.⁹

In this study, we also have examined the question whether renal elimination of pancuronium is a determining factor in pancuronium requirement during constant infusion on demand and whether pancuronium excretion is substantially modified by the variations in renal function associated with cardiopulmonary bypass, mannitol administration, hypothermia, and hemodilution. We noted that pancuronium requirement is not firmly related to the quantity of pancuronium eliminated in the urine. In particular, in Period III the urinary excretion of pancuronium and of its metabolites largely exceeded the quantity of pancuronium infused. Thereafter, in Periods IV and V, while pancuronium requirements increased, pancuronium elimination in urine decreased slightly. As observed in this study, creatinine clearance is altered by CPB. This apparent reduction of renal performance at the end of CPB probably results from slight diminution in renal perfusion due either to the non-pulsatile flow of the cardiopulmonary bypass machine or to the progressive impairment of renal function due to alterations in such variables as the plasma concentration of catecholamines, vasopressin, and renin occurring during CPB.^{10–14}

In summary, the use of on-demand continuous infusion of pancuronium, modified as necessary to produce a constant degree of paralysis in a skeletal muscle group, has made possible the quantitative evaluation of pancuronium requirement during cardiac surgery with CPB, hemodilution, and hypothermia. The present results indicate that variation in muscle temperature is an important determinant of pancuronium requirement and of plasma concentration. However, during CPB these temperature-induced variations can be modified by the effect of hemodilution which decreases muscle relaxant plasma concentration: this is more or less compensated by an increase in the plasma of the free drug fraction. From a practical point of view, during CPB, pancuronium requirements increase at two specific moments: initiation of extracorporeal circulation and rewarming of the patient.

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