Anesthesiology
60:569–574, 1984

Pharmacokinetics, Placental Transfer, and Neonatal Effects of Vecuronium and Pancuronium Administered during Cesarean Section

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Vecuronium and pancuronium were compared for placental transfer, pharmacokinetic variables, and neonatal effects during cesarean section under general anesthesia. Eighteen women underwent rapid-sequence intravenous induction using *d*-tubocurarine, succinylcholine, thiopental, and oxygen. Immediately after tracheal intubation, an intravenous injection of vecuronium (n = 11) or pancuronium (n = 7), 0.04 mg/kg, was given. Maternal venous blood samples were obtained before induction and at frequent intervals for 4 h after administration of vecuronium or pancuronium. Also, maternal venous and umbilical-cord arterial and venous blood samples were obtained at delivery. To describe placental transfer and maternal pharmacokinetics of the drugs, serum drug concentrations were determined using single-ion-monitoring mass spectrometry. The Apgar score and Neurologic and Adaptive Capacity Score (NACS) were used to evaluate neonatal condition. Both drugs crossed the placenta, as demonstrated by low concentrations of vecuronium (8.5–26.4 ng/ml) or pancuronium (12.2–34.2 ng/ml) found in umbilical venous blood. At delivery, the ratio of the drug concentration in umbilical venous blood to that in maternal venous blood was 0.11 ± 0.02 for vecuronium and 0.19 ± 0.03 for pancuronium. Vecuronium had a more rapid clearance (6.4 ± 0.4 ml · kg^{-1} · min^{-1}, mean ± SE) and a shorter elimination half-life (36 ± 1.8 min) than pancuronium (3.0 ± 0.1 ml · kg^{-1} · min^{-1} and 72 ± 6 min, respectively). No other pharmacokinetic differences were found between the drugs. Neonatal outcome was not affected adversely by either muscle relaxant, as assessed by Apgar scores and NACSs. The short duration of action, the minimal placental transfer, and the apparent lack of clinical neuromuscular effects on the newborn suggest that vecuronium should be a useful muscle relaxant for cesarean section. (Key words: Anesthesia: obstetric. Neurobehavior: neonatal. Neuromuscular relaxants: pancuronium; vecuronium. Pharmacokinetics.)

SKELETAL MUSCLE RELAXATION frequently is required in lightly anesthetized patients undergoing cesarean section. Although pancuronium, *d*-tubocurarine, and succinylcholine are used currently, each has well-known disadvantages. Vecuronium (ORG NC45, Norcuron™) is a monoquaternary homologue of pancuronium that has no vagolytic, histamine-releasing, or autonomic effects.[1] Although vecuronium and pancuronium have similar onset times, the former has a shorter duration of action[2] and no apparent cardiovascular effects.[3] These advantages make vecuronium a desirable skeletal muscle relaxant for cesarean section, provided it does not adversely affect the neonate. To evaluate this possibility, we compared the maternal pharmacokinetics, placental transfer, and neonatal effects of these two drugs when administered before delivery of the infant by cesarean section.

Materials and Methods

We studied 18 healthy women at term who requested general anesthesia for cesarean section. Indications for cesarean section were previous cesarean section, breech or transverse presentation, failure of labor to progress, or cephalopelvic disproportion. Patients demonstrating evidence of fetal distress were excluded from study. We obtained institutional approval and informed consent from each patient.

All patients were premedicated with glycopyrrolate, 0.2 mg iv, and magnesium and aluminum hydroxide, 30 ml orally, 15–60 min before induction of anesthesia. Indwelling intravenous catheters were inserted in both arms, one for sampling of venous blood and the other for ad-

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Received from the Departments of Anesthesia, San Francisco General Hospital, San Francisco, California; the University of California, San Francisco, California; and the University of Southern California, Los Angeles, California. Accepted for publication November 29, 1983. Supported in part by Organon, Inc., and the Anesthesia–Pharmacology Research Foundation. Presented in part at the annual meeting of the American Society of Anesthesiologists, Las Vegas, October 1982.

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TABLE 1. Comparison of Patients Given Vecuronium or Pancuronium before Cesarean Delivery

	Vecuronium (n = 11)	Pancuronium (n = 7)
Age (yr)	26.5 ± 1.6	28.1 ± 3.2
Weight (kg)	73.3 ± 4.2	74.1 ± 4.3
Weeks of gestation	39.9 ± 0.4	40.0 ± 0.4
Time from induction of anesthesia to delivery (min)	8.1 ± 0.8	11.8 ± 1.0*
Time from administration of drug to delivery (min)	6.2 ± 0.7	10.3 ± 1.0*
Time from uterine incision to delivery (s)	138 ± 27	120 ± 22

Values are mean ± SE.
* Significantly different from vecuronium ($P < 0.05$).

ministering drugs and fluids. Patients were placed in the supine position, and the uterus was displaced leftward to avoid aortocaval compression. The blood-sampling catheter was kept patent by slowly infusing an isotonic saline solution containing heparin 1.0 unit/ml. After administering *d*-tubocurarine, 3 mg iv, and having the patient breathe 100% oxygen, we induced general anesthesia with thiopental, 4 mg/kg, followed by succinylcholine, 1.5 mg/kg. The trachea then was intubated while cricoid pressure was applied. Pancuronium or vecuronium, 0.04 mg/kg, then was administered iv. This dose of pancuronium is 1.8 times its ED_{50} (dose producing a 50% depression of evoked twitch tension), while the dose of vecuronium is 2.7 times its ED_{50} during anesthesia with nitrous oxide and halothane.[2] The relatively larger dose of vecuronium was used to elicit possible adverse effects on the infant resulting from placental drug transfer.

Before cesarean delivery, anesthesia was maintained with 50% nitrous oxide in oxygen. After delivery, we administered butorphanol, 2–5 mg iv. Neuromuscular function was monitored using a peripheral nerve stimulator. When additional relaxation was necessary, *d*-tubocurarine was given; *d*-tubocurarine does not interfere with the assay of pancuronium and vecuronium. At the conclusion of surgery, neuromuscular blockade was antagonized with neostigmine, 3–5 mg iv, and either atropine, 1.0 mg, or glycopyrrolate, 0.6–1.0 mg iv.

TABLE 2. Comparison of Newborns Whose Mothers Were Given Vecuronium or Pancuronium before Cesarean Delivery

	Vecuronium (n = 11)	Pancuronium (n = 7)
Mean (±SE) birth weight (g)	3459 ± 167	4020 ± 97*
Apgar scores of 8–10†:		
At 1 min (%)	45	57
At 5 min (%)	91	100
NACSs of 35–40†:		
At 15 min (%)‡	73	29
At 2 h (%)	73	57
At 24 h (%)	100	100

* Significantly different from vecuronium ($P < 0.05$).
† Apgar scores of 8–10 and Neurologic and Adaptive Capacity Scores (NACSs) of 35–40 denote a vigorous baby.
‡ A NACS was not obtained at 15 min for infant 6 in the vecuronium group and was assumed to be less than 35. This infant was delivered 293 s after uterine incision and required endotracheal intubation and positive-pressure ventilation. Apgar scores at 1 and 5 min were 1 and 6, respectively.

Maternal venous blood samples were collected for determination of concentrations of muscle relaxant before induction of anesthesia and 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210, and 240 min after administration of pancuronium or vecuronium. At delivery, maternal venous blood and umbilical arterial and umbilical venous blood samples were obtained from a doubly clamped segment of umbilical cord for analysis of muscle relaxant concentrations and acid–base status. After collection, blood samples immediately were placed in ice. Samples were centrifuged and the serum frozen at −70°C until analyzed.

The condition of the infant was evaluated using Apgar scores at 1 and 5 min, analysis of umbilical-cord blood gases, and the Neurologic and Adaptive Capacity Scores (NACSs)[4] at 15 min, 2 h, and 24 h after birth. The Apgar score gives a maximum total score of 10; we considered an infant scoring 8 or greater as vigorous. The NACS gives a maximum score of 40. Choosing 35–40 as the score denoting a vigorous baby, we determined the percentage of infants scoring 35 or higher and compared the two study groups at 15 min, 2 h, and 24 h. We also determined the percentage of infants having high scores (a score of 2) on each of the individual test items of passive and active tone. Apgar scores and NACSs were obtained by an investigator who did not know which muscle relaxant had been administered.

Serum concentrations of pancuronium and vecuronium were measured using single-ion-monitoring mass spectrometry,[5] deuterated pancuronium or vecuronium being the internal standard. This assay measures only the unmetabolized parent compound, with a sensitivity to 2.0 ng/ml of serum and a coefficient of variation less than 10% (at all drug concentrations).

Data were fitted to both two- and three-compartment open pharmacokinetic models using a weighted, nonlinear, least-squares regression. Values were weighted by $(\text{serum concentration})^{3/2}$. A two-compartment model was selected using the technique of Boxenbaum *et al.*[6] The following parameters were determined by standard formulas[7]: distribution half-life ($t_{1/2}\alpha$), elimination half-life ($t_{1/2}\beta$), volume of distribution at steady state (Vd_{ss}), and total clearance (Cl).

Data are presented as mean values and the standard error of the mean. Statistical comparisons of the data were made using unpaired Student's *t* test for the demographic data, mean time intervals prior to delivery,

blood gases at delivery, serum concentrations at delivery, and pharmacokinetic data. Apgar scores and NACSs were analyzed using a Fisher exact test. Differences were considered significant when $P < 0.05$.

Results

Eleven patients received vecuronium and seven patients, pancuronium. Both groups were similar in age, weight, and weeks of gestation (table 1). Two patients in each group underwent elective repeat cesarean section. Transverse lie or breech presentation was the condition warranting cesarean section for nine patients given vecuronium and for one patient given pancuronium; all were in labor. Four patients given pancuronium had cesarean section because of cephalopelvic disproportion or failure of labor to progress.

Table 2 compares birth weight, Apgar scores, and NACSs for infants of mothers given vecuronium or pancuronium. Infants of mothers given vecuronium weighed significantly less than infants of mothers given pancuronium. However, these two groups did not differ significantly in Apgar scores and NACSs, including specific tests of active and passive tone (table 3). Maternal venous and umbilical-cord blood gases at delivery were within the normal range; there were no statistically significant differences between patients given vecuronium and those given pancuronium.

Both vecuronium and pancuronium crossed the placenta. Concentrations of vecuronium and pancuronium in maternal and umbilical cord blood at the time of delivery are presented in table 4. The concentration of muscle relaxant was not determined for two patients in each group because of technical errors in collecting or handling the blood samples. We were able to obtain an adequate volume of umbilical arterial blood for analysis of drug concentrations from only five patients. At delivery, the concentration of vecuronium in maternal venous blood was significantly higher than the concentration of pancuronium. Patients given vecuronium had shorter times from induction of anesthesia to delivery and from administration of the study drug to delivery, than did patients given pancuronium (table 1). The ratio of drug concentration in umbilical venous blood to that in maternal venous blood (UV/MV) was significantly greater for pancuronium (0.19) than for vecuronium (0.11). The coefficient of determination, r^2, between UV/MV and time for administration of study drug to delivery was 0.37 ($P = 0.08$) for vecuronium and 0.01 ($P = 0.8$) for pancuronium. Pancuronium and vecuronium did not differ significantly in $t_{1/2}\alpha$ or Vd_{ss} (table 5). However, $t_{1/2}\beta$ was two times higher for pancuronium than for vecuronium, and Cl of pancuronium was half that of vecuronium.

TABLE 3. Percentages of Infants Who Scored 2 on NACS Test Items Evaluating Passive and Active Tone 15 Min after Birth*

	Vecuronium (n = 10)† (%)	Pancuronium (n = 7) (%)
Tests of passive tone		
Scarf sign‡	100	71
Recoil of elbows	50	43
Popliteal angle	60	71
Recoil of lower limbs	70	71
Tests of active tone		
Active contraction of neck flexors	90	71
Active contraction of neck extensors	80	71
Palmar grasp	90	43
Response to traction	90	43
Supporting reaction	50	57

* No significant difference between the two groups on any test item, as determined by Fisher's exact test. A score of 2 is normal.

† A Neurologic and Adaptive Capacity Score (NACS) was not obtained for infant 6 at 15 min because of need to resuscitate infant.

‡ "Scarf sign"; the arm should encircle the neck like a scarf. The infant is given a score of 2 if the elbow does not reach midline.

The maternal neuromuscular effects of vecuronium and pancuronium were not studied because succinylcholine was administered before intubation. Nondepolarizing drugs are potentiated when they are given after succinylcholine.[8,9] The neuromuscular blockade was reversed before complete duration of neuromuscular blockade could be assessed.

TABLE 4. Serum Concentrations of Vecuronium and Pancuronium at Delivery

Patient No.	Time from Relaxant to Delivery (min)	Drug Levels in Blood Samples: Maternal Vein (ng/ml)	Umbilical Vein (ng/ml)	Umbilical Artery (ng/ml)	UV/MV
Vecuronium					
1	5.7	112	15.5	8.8	0.138
2	7.8	181	26.4	—	0.146
3	6.8	172	17.7	—	0.103
4	9.4	113	23.1	—	0.204
5	4.8	152	8.5	—	0.056
6	8.2	170	20.6	—	0.121
7	4.0	192	22.0	—	0.115
8	6.2	181	10.2	9.4	0.056
9	7.3	187	17.1	—	0.091
Mean	6.7	162	17.9	9.1	0.11
±SE	±0.6	±10	±2.0		±0.02
Pancuronium					
1	10.6	138	14.4	2.21	0.104
2	14.2	130	34.2	15.5	0.263
3	7.5	99	26.2	—	0.265
4	8.6	83	12.2	1.28	0.148
5	12.2	127	21.1	—	0.166
Mean	10.6	115	21.6	6.33	0.19
±SE	±1.2*	±10.5*	±4.0	±0.5	±0.03*

UV/MV = ratio of the drug concentration in umbilical venous blood to the drug concentration in maternal venous blood.

* Significantly different from vecuronium, $P < 0.05$.

TABLE 5. Pharmacokinetics of Vecuronium and Pancuronium Administered Intravenously before Cesarean Delivery

	Vecuronium (n = 5)	Pancuronium (n = 3)
Distribution half-life (min)	5.1 ± 0.9	3.8 ± 1.5
Elimination half-life (min)	36 ± 1.8	72 ± 6*
Volume of distribution at steady state (ml/kg)	251 ± 7.0	283 ± 28
Total clearance ($ml \cdot kg^{-1} \cdot min^{-1}$)	6.4 ± 0.4	3.0 ± 0.1†

Values are mean ± SE.
* Significantly different from vecuronium, $P < 0.01$.
† Significantly different from vecuronium, $P < 0.001$.

Discussion

Compared with their concentrations in maternal blood, the concentrations of vecuronium and pancuronium in the umbilical vein are low. In addition, the concentrations in the umbilical artery are lower. These differences suggest that at the time of sampling, muscle relaxants were undergoing distribution within the infant. The effective concentrations at the neuromuscular junction were probably very low and therefore clinically insignificant. It is the unbound portion of drug in the blood that is available for binding to receptor sites and, thus, for exerting pharmacologic effects. Pancuronium is not highly protein bound; the free fraction in newborns and their mothers is 91% and 89%, respectively.[10] Vecuronium also is probably not highly protein bound to any significant extent. Only one muscle relaxant, *d*-tubocurarine, has been examined regarding age-related changes in the venous plasma concentrations that produce neuromuscular blockade.[11] For *d*-tubocurarine, the plasma concentration that produces 50% neuromuscular blockade during anesthesia with nitrous oxide and halothane is 50% lower in neonates than in adults. The plasma concentrations of vecuronium and pancuronium that cause 50% block of the twitch response in adults during anesthesia with nitrous oxide and halothane are 94 ng/ml and 88 ng/ml, respectively.[5] If neonates developed 50% neuromuscular blockade at one-half these concentrations, the concentrations of muscle relaxants obtained in this study probably would not result in significant neuromuscular depression.

We found no evidence of adverse neonatal effects with either drug. Other studies also have reported no clinical evidence of myoneural blockade in infants whose mothers had received muscle relaxants before delivery[12–16]; these conclusions were based on Apgar scores and general observations. Infants may have alterations in neurologic and behavioral function despite normal Apgar scores. Tests of neurologic and behavioral function include the Early Neonatal Neurobehavioral Scale (ENNS),[17] the Neonatal Behavioral Assessment Scale (NBAS),[18] and the NACS.[4] We selected the NACS because it places more emphasis on muscle tone—both passive and active—than the other tests.[19] We found no significant differences in Apgar scores and NACSs between infants of mothers given vecuronium or pancuronium. In addition, with the exception of the supporting reaction, there were no significant differences in NACS test items for passive and active tone at 15 min for infants of mothers given vecuronium and pancuronium compared with infants delivered by vaginal delivery whose mothers received minimal anesthesia.[20] Neither the Apgar score nor the NACS is a specific test of neuromuscular transmission (such as the electromyogram or twitch depression); both can be affected by a variety of factors including drugs used for anesthesia, the length of anesthesia, and fetal hypoxia.

The cardiovascular effects of vecuronium and pancuronium were not studied. The study drugs were administered immediately following intubation, a time when there are cardiovascular changes related to intubation, skin incision, and other drugs. Other studies[3,21] report

TABLE 6. A Summary of Studies of Placental Transfer of Vecuronium and Pancuronium

Dose (mg/kg)	No. of Patients	Time from Drug to Delivery (min)	Drug Levels in Blood Samples: Maternal Vein (ng/ml)	Drug Levels in Blood Samples: Umbilical Vein (ng/ml)	UV/MV	Reference
Vecuronium						
0.04	9	6.7	162	18	0.11	This study
0.06–0.08	20	9.4	390	40	0.11	Demetriou *et al.*[16]
Pancuronium						
0.04	5	10.6	115	22	0.19	This study
0.05	23	4.2	420	80	0.21	Abouleish *et al.*[15]
0.06	10	10.1	306	68	0.24	Booth *et al.*[22]
0.10	26	12.9	510	120	0.26	Abouleish *et al.*[15]
0.06–0.10	33	3–36	340	70	0.22	Duvaldestin *et al.*[14]

UV/MV = ratio of the drug concentration in umbilical venous blood to the drug concentration in maternal venous blood.

minimal cardiovascular changes following administration of vecuronium, while pancuronium produces significant increases in heart rate and blood pressure.

Other investigators[14-16,22] have studied the placental transfer of vecuronium and pancuronium (table 6). Although our values for UV/MV for vecuronium and pancuronium are in agreement with these studies, our measured concentrations of vecuronium and pancuronium are lower, even adjusting for the different drug doses administered to the mother and times from drug to delivery. This may be due to differences in assay methods. Booth *et al.*,[22] Duvaldestin *et al.*,[14] Abouleish *et al.*,[15] and Demetriou *et al.*[16] used a fluorometric assay that does not discriminate between the unchanged drug and its hydrolyzed, relatively inactive, metabolites.[23] In contrast, single-ion-monitoring mass spectrometry measures only the parent compound and not the metabolites.

Studying pharmacokinetics of pancuronium, Duvaldestin *et al.*[14] compared women undergoing cesarean section with patients undergoing elective abdominal surgery (controls). Mean (±SE) $t_{1/2}\beta$ of pancuronium was significantly shorter for patients undergoing cesarean section (114 ± 27 min) than for controls (146 ± 38 min). There were no significant differences in $t_{1/2}\alpha$ or Vd_{ss}. We found these same pharmacokinetic differences between nonpregnant patients[5] and patients undergoing cesarean section, for both vecuronium and pancuronium. For both drugs, Cl was lower for nonpregnant patients than for patients undergoing cesarean section (5.2 *vs.* 6.4 $ml \cdot kg^{-1} \cdot min^{-1}$ for vecuronium, 1.8 *vs.* 3.0 $ml \cdot kg^{-1} \cdot min^{-1}$ for pancuronium). Because the values for Vd_{ss} were similar for nonpregnant and cesarean section patients, $t_{1/2}\beta$ was shorter in the latter (71 *vs.* 36 min for vecuronium, 140 *vs.* 72 min for pancuronium).

This increase in Cl may result from several factors. First, during cesarean section the acute loss of approximately one liter of blood and the subsequent volume replacement result in dilution of the drug in the body. However, the increase in Cl that occurs with pregnancy is probably greater than can be explained by these acute fluid shifts. Second, during cesarean delivery, the infant and placenta are removed from the mother; thus, any drug in these tissues need not be cleared by the usual mechanisms. This study has demonstrated that only small quantities of drug enter the fetus, and, therefore, that removal of the fetus is not likely to alter Cl markedly. Finally, during pregnancy, high levels of circulating progesterone may stimulate the hepatic microsomal mixed function oxidase system and thereby increase the rate of biotransformation.[24] Hepatic and renal elimination of other drugs has been demonstrated to increase during pregnancy.[25] Perhaps more rapid metabolism of vecuronium and pancuronium during pregnancy results in the accelerated clearance from the plasma.

In summary, vecuronium and pancuronium do cross the placenta, the UV/MV concentration of vecuronium being half that of pancuronium. However, at the doses studied, these muscle relaxants did not appear to affect the newborn infant adversely. In patients undergoing cesarean section, vecuronium had greater Cl and a shorter $t_{1/2}\beta$ than did pancuronium. In addition, for both drugs, $t_{1/2}\beta$ was shorter in patients undergoing cesarean section than in nonpregnant patients undergoing surgery. Because of its more rapid clearance, short duration of action, and minimal placental transfer, vecuronium may be a useful muscle relaxant for patients undergoing cesarean section under general anesthesia.

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