

Pharmacokinetics and Pharmacodynamics of Vecuronium (ORG NC45) and Pancuronium in Anesthetized Humans

Roy Cronnelly, M.D., Ph.D.,* Dennis M. Fisher, M.D.,† Ronald D. Miller, M.D.,‡ Peter Gencarelli, M.D.,†
Lang Nguyen-Gruenke, Ph.D.,§ Neal Castagnoli, Jr., Ph.D.¶

The pharmacokinetics and pharmacodynamics of vecuronium (25–50 $\mu\text{g}/\text{kg}$) and pancuronium (25–50 $\mu\text{g}/\text{kg}$) were determined in nine ASA class I or II patients anesthetized with nitrous oxide and halothane. Force of thumb adduction in response to supramaximal stimulation of the ulnar nerve was quantified and recorded. Serum concentrations of the muscle relaxants were determined for eight hours after their administration using a mass spectrometry assay. Data were analyzed by nonlinear regression and fit to a three-compartment pharmacokinetic model and a four-compartment pharmacodynamic model. Vecuronium had a more rapid clearance ($5.2 \pm 0.7 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; mean \pm SD) and a shorter elimination half-life ($71 \pm 20 \text{ min}$) as compared with pancuronium ($1.8 \pm 0.4 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; $140 \pm 25 \text{ min}$). No other pharmacokinetic differences were found between the drugs. Pharmacodynamic analysis showed that the plasma concentration at steady state which produced a 50% neuromuscular blockade (Cp_{50} , 50) was similar for vecuronium and pancuronium. The authors conclude that the drugs are equivalent in their onset and potency; however, the more rapid clearance and shorter elimination half-life for vecuronium provides a kinetic basis for its shorter duration of neuromuscular blockade as compared with pancuronium. (Key words: Pharmacokinetics: kinetics; models. Neuromuscular relaxants: pancuronium; vecuronium (ORG NC45); vecuronium. Potency: Cp_{50} (50))

VECURONIUM (ORG NC45, Norcuron™) is a monoquaternary homologue of pancuronium with a shorter duration of action and fewer cardiovascular effects as compared with pancuronium.^{1,2} Perhaps the shorter duration of action of vecuronium is a result of a more rapid clearance from plasma than pancuronium. To explore this possibility we compared the pharmacokinetics and pharmacodynamics of vecuronium and pancuronium using a new sensitive mass spectrometric assay.

* Assistant Professor, Anesthesia and Pharmacology.

† Research Fellow in Anesthesia.

‡ Professor and Vice Chairman, Anesthesia, and Professor of Pharmacology.

§ Assistant Research Chemist.

¶ Professor of Chemistry and Pharmaceutical Chemistry.

Received from the Department of Anesthesia, University of California, San Francisco, California. Accepted for publication September 20, 1982. Supported in part by Organon, Inc., the Anesthesia-Pharmacology Research Foundation and NIH Grant R01GM 24603-3. Presented in part at the annual meeting of the International Anesthesia Research Society, San Francisco, California, March 1982.

Address reprint requests to Dr. Cronnelly: Department of Anesthesia, S-436, University of California, San Francisco Medical Center, San Francisco, California 94143.

Methods

The study was approved by our Committee on Human Research and informed consent was obtained from nine patients of both sexes, ASA Class I and II, and 29–69 years of age. All patients had normal laboratory values for serum electrolytes, blood urea nitrogen, creatinine, serum glutamic oxaloacetic transaminase, lactic acid dehydrogenase, and alkaline phosphatase. The patients underwent surgical procedures associated with minimal blood loss and were receiving no medications known to alter the response to muscle relaxants. Anesthesia was induced with 1–2 mg/kg thiopental iv, and maintained with nitrous oxide, 60% in oxygen, and halothane, 0.5–0.7%, end-tidal concentration as measured by mass spectrometry. Endotracheal intubation was accomplished without the use of muscle relaxants. Ventilation was controlled to maintain an end-tidal P_{CO_2} of 30–40 mmHg, and esophageal temperature was maintained between 35–37° C. Supramaximal square-wave pulses of 0.15-ms duration were delivered at 0.15 Hz to the ulnar nerve at the wrist through 27-gauge needle electrodes. The resultant force of thumb adduction was quantified with a Grass® FT-10 force displacement transducer and recorded on a polygraph. Following at least 30 min of stable end-tidal halothane concentrations, pancuronium ($n = 4$, 25–50 $\mu\text{g}/\text{kg}$) or vecuronium ($n = 5$, 25–50 $\mu\text{g}/\text{kg}$) was infused iv over a 10-min period. Venous blood was then sampled (3 ml/sample) from the contralateral arm at 2, 4, 6, 8, 10, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, and 480 min after the start of infusion, and again at 24 h.

Drug concentrations were measured using selective ion monitoring mass spectrometry as described in the appendix. This assay is sensitive to 2.0 ng/ml with a coefficient of variation of 10% and measures only the unmetabolized, parent compound.

Data were fitted to both two- and three-compartment open pharmacokinetic models modified for an infusion³ using a nonlinear least-square regression.⁴ A three-compartment model was selected by the technique of Boxenbaum *et al.*⁵ The following parameters were determined using standard formulas: rapid distribution half-life ($t_{1/2\pi}$), distribution half-life ($t_{1/2\alpha}$), elimina-

TABLE 1. Pharmacokinetic and Pharmacodynamic Values (Means \pm SD)

	N	$t_{1/2\pi}$ (min)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	V_1 (l/kg)	Vd_{ss} (l/kg)	Cl (ml \cdot kg ⁻¹ \cdot min ⁻¹)	Cp_{ss50} (ng/ml)
Pancuronium	4	2.7 \pm 1.2	20 \pm 9	140 \pm 25	0.05 \pm .02	0.26 \pm .07	1.8 \pm 0.4	88 \pm 34
Vecuronium	5	2.2 \pm 1.4	13 \pm 8	71* \pm 20	0.05 \pm .02	0.27 \pm .04	5.2* \pm 0.7	94 \pm 33

*Different from pancuronium.

tion half-life ($t_{1/2\beta}$), central compartment volume (V_1), volume of distribution at steady-state (Vd_{ss}), and clearance (Cl).⁶

The magnitude of neuromuscular blockade was measured from onset to complete recovery of the blockade and these data fitted to estimates of the kinetic parameters according to the technique of Sheiner *et al.*⁷ This allowed determination of the steady-state concentration that results in 50% paralysis (Cp_{ss50}). Mean values for pharmacokinetic and pharmacodynamic parameters were compared by Student's *t* test.⁸ Differences were considered significant at $P < 0.05$.

Results

Measurable concentrations of pancuronium could be found in serum at 24 h (approximately 1 ng/ml), whereas concentrations of vecuronium fell below our limits of sensitivity after 5–6 h. Vecuronium had a significantly faster clearance rate and a shorter elimination half-life compared with pancuronium. No other phar-

macokinetic differences were found between vecuronium and pancuronium (table 1). Typical data for the relationship between plasma concentration and effect are displayed in figures 1 and 2 for pancuronium and vecuronium, respectively. The adequacy of data characterization by the model is evidenced by the close approximation of the fitted functions to the patient data. Pharmacodynamic analysis demonstrated no difference between the drugs in terms of Cp_{ss50} (table 1).

Discussion

We determined that vecuronium has a shorter elimination half-life and more rapid clearance than pancuronium which probably accounts for the shorter duration of its neuromuscular blockade. Pharmacokinetic analyses of neuromuscular relaxants depend on the existence of sensitive and specific assays such as the radioimmunoassay technique for *d*-tubocurarine.⁹ All previous studies of pancuronium used a fluorometric

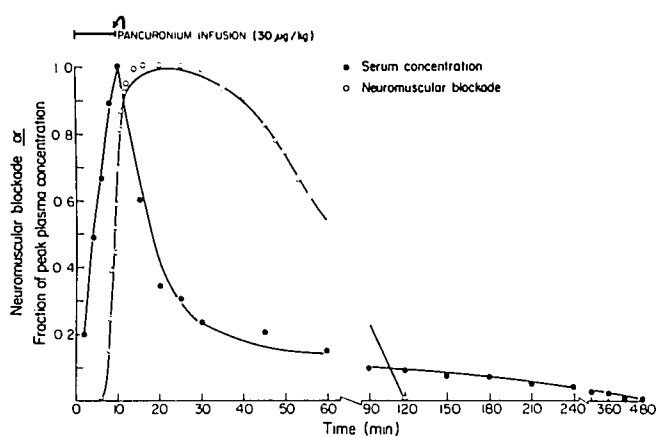


FIG. 1. Data from a patient anesthetized with halothane in whom pancuronium was infused over a 10-minute period. Plasma concentration is plotted as the fraction of the peak plasma concentration observed. Neuromuscular blockade is plotted from 0 = no paralysis to 1 = 100% paralysis. The solid lines represent the fitted function as determined by nonlinear regression, while the open and closed circles represent actual plasma concentrations and measurements of the magnitude of neuromuscular blockade.

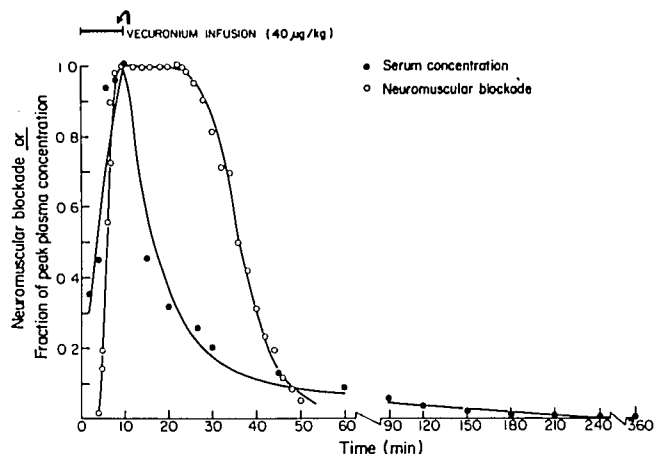


FIG. 2. Data from a patient anesthetized with halothane in whom vecuronium was infused over a 10-minute period. Plasma concentration is plotted as the fraction of the peak plasma concentration observed. Neuromuscular blockade is plotted from 0 = no paralysis to 1 = 100% paralysis. The solid lines represent the fitted function as determined by nonlinear regression, while the open and closed circles represent actual plasma concentrations and measurements of the magnitude of neuromuscular blockade.

method which is nonspecific in that it does not discriminate between metabolites, structural analogues like vecuronium and the parent compound, and lacks sensitivity in a clinically useful range, *i.e.*, 5 ng/ml or less. Interestingly, the estimates of distribution volumes, elimination half-lives, and clearance rates obtained in those studies are not much different from our study using a specific mass spectral analysis.¹⁰⁻¹² Realizing that a nonspecific assay (fluorometric) yields similar data to the specific assay (mass spectrometric) indirectly suggests that the contribution of metabolites to the previously measured levels of pancuronium was insignificant.

Although vecuronium is a monoquatary compound and more lipid-soluble than pancuronium, the steady-state distribution volumes ($V_{d_{ss}}$) do not exceed extracellular fluid volumes for either drug. The similarities in distribution half-lives and distribution volumes may explain why the onset of action is the same for both drugs.¹

We determined that the clearance of vecuronium is three times greater than that of pancuronium. Furthermore, the pharmacokinetics and pharmacodynamics of vecuronium are not altered in the absence of renal function in animals¹³ or humans.¹⁴ Therefore, non-renal clearance, perhaps via hepatic mechanisms must be of greater importance for vecuronium than for pancuronium. Consistent with this prediction, a vecuronium-induced neuromuscular blockade was prolonged by exclusion of the liver from the circulation in cats.¹⁵ Also, in rats, over 60% of an intravenous dose of vecuronium may be found unchanged in the bile compared with only 15% for pancuronium.¹⁶ The non-renal elimination of vecuronium offers an advantage over other nondepolarizing relaxants in patients with renal failure; however, its effects in patients with cirrhosis or biliary obstruction have not yet been determined.

Our pharmacodynamic analysis showed no difference in Cp_{ss50} between pancuronium and vecuronium. In view of the similarity in distribution volumes and distribution half-lives, this suggests that the two drugs are equipotent. Yet, potency ratios for vecuronium varying from 1.0 to 1.74 have been reported previously.^{1,17} These discrepancies may stem from the variety of anesthetic conditions used during previous determinations. We maintained the anesthetic level of halothane within a narrow range to minimize this variability.

We conclude that pancuronium and vecuronium are equivalent in their onset time of neuromuscular blockade and potency; however, the more rapid clearance and shorter elimination half-life found for vecuronium provides a kinetic basis for its short duration of neuromuscular blockade.

References

1. Fahey MR, Morris RB, Miller RD, Sohn YJ, Cronnelly R, Gen-carelli P: Clinical pharmacology of ORG NC45 (Norcuron). *ANESTHESIOLOGY* 55:6-11, 1981
2. Morris RB, Wilkinson PL, Miller RD, Cahalan M, Quasha A: Cardiovascular effects of ORG NC45 (Norcuron) in patients undergoing coronary artery bypass grafting. *ANESTHESIOLOGY* 55:A205, 1981
3. Loo JCK, Riegelman S: Assessment of pharmacokinetic constants from postinfusion blood curves obtained after IV infusion. *J Pharm Sci* 59:53-55, 1970
4. Dixon WJ; Ed: *BMDP Statistical Software*. Berkeley, University of California Press, 1981, pp 305-329
5. Boxenbaum H, Riegelman S, Elashoff R: Statistical estimation in pharmacokinetics. *J Pharmacokinet Biopharm* 2:123-148, 1974
6. Gibaldi M, Perrier D: *Pharmacokinetics*. New York, Dekker, 1975, pp 48-55, 66-69, 72-74, 175-180
7. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J: Simultaneous modeling of pharmacokinetics and pharmacodynamics; application to *d*-tubocurarine. *Clin Pharmacol Ther* 24:358-371
8. Zar J: *Biostatistical Analysis*. Englewood Cliffs, Prentice Hall, 1974
9. Horowitz PE, Spector S: Determination of serum *d*-tubocurarine concentrations by radioimmunoassay. *J Pharmacol Exp Ther* 185:94-100, 1973
10. Buzello W, Agoston S: Kinetics of intercompartmental disposition and excretion of tubocurarine, gallamine, alcuronium and pancuronium in patients with normal and impaired renal function. *Anaesthetist* 27:319, 1978
11. Somogyi AA, Shanks CA, Triggs EJ: The effect of renal failure on the disposition and neuromuscular blocking action of pancuronium bromide. *Eur J Clin Pharmacol* 12:23-291, 1977
12. Miller RD, Agoston S, Booij LHDJ, Kersten UW, Crul JF, Ham J: The comparative potency and pharmacokinetics of pancuronium and its metabolites in anesthetized man. *J Pharmacol Exp Ther* 207:539-543, 1978
13. Durant NN, Houwertjes MC, Agoston S: Renal elimination of ORG NC45 and pancuronium. *ANESTHESIOLOGY* 51:S267, 1979
14. Fahey MR, Morris RB, Miller RD, Nguyen TL, Upton RA: Pharmacokinetics of ORG NC45 (norcuron) in patients with and without renal failure. *Br J Anaesth* 53:1049-1052, 1981
15. Durant NN, Houwertjes MC, Agoston S: Hepatic elimination of ORG NC45 and pancuronium. *ANESTHESIOLOGY* 51:S267, 1979
16. Upton RA, Nguyen TL, Miller RD, Castagnoli N Jr: Renal and biliary elimination of vecuronium ORG NC45 and pancuronium in rats. *Anesth Analg (Cleve)* 61:313-316, 1982
17. Kreig N, Crul JF, Booij LHDJ: Relative potency of ORG NC45, pancuronium, metocurine, and tubocurarine in anesthetized man. *Br J Anaesth* 52:783-788, 1980

APPENDIX

Serum Assay for Pancuronium and Vecuronium by Chemical Ionization Mass Spectrometry

Quantitative estimations of the serum levels of pancuronium and vecuronium were achieved by a stable isotope di-

lution assay which employs pancuronium- d_6 or vecuronium- d_6 (bisacetyl- d_6) as the internal standard and chemical ionization mass spectrometry (1.0 mmHg, isobutane) as the determinative step. The assay depends on the thermal bis-N-demethylation of pancuronium or the N-demethylation of vecuronium which leads in both cases to the formation of the corresponding volatile bisamine.

To a 1-ml serum sample is added internal standard (300 ng) in 0.1 ml acetonitrile, acetonitrile (1.5 ml), and dichloromethane (8 ml). After gentle mixing, the dichloromethane layer is separated and evaporated to dryness. The residue in 1 ml water is washed with ether (2×2 ml) and after the addition of saturated potassium iodide (1 ml) the resulting solution is extracted with dichloromethane (5 ml). The residue obtained after removing the dichloromethane is transferred in acetonitrile to the ceramic tip of the direct insertion probe

of an AELI MS 902 mass spectrometer. The probe then is inserted into the preheated (about 150°C) ionization chamber and the ion currents at m/z 543 and m/z 549 due to impurities but not drug are monitored. When impurities are no longer detected at these masses, the probe is withdrawn and the ionization chamber temperature is increased to about 170°C . The probe then is reinserted and the ion currents at m/z 543 (MH^+ for the bisamine derived from pancuronium-d or vecuronium- d_6 or vecuronium- d_6) are determined by selected ion monitoring. The actual concentrations of the drug are calculated by comparing the ion current ratios with the corresponding ratios of a calibration curve prepared on the same day from blank serum samples containing known amounts (0 to 500 ng) of pancuronium or vecuronium and 300 ng of the deuterated internal standard. The assay can detect accurately levels of pancuronium or vecuronium as low as 2 ng/ml.

NOTICE TO COPIERS

The appearance of the code at the bottom of the first page of an article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per-copy fee through the Copyright Clearance Center, Inc., 21 Congress Street, Salem, Massachusetts 01970, for copying beyond that permitted by Sections 107 or 108 of the U. S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale.