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 μg/kg) and pancuronium (25–50 μg/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 ± 0.7 ml·kg⁻¹·min⁻¹; mean ± SD) and a shorter elimination half-life (71 ± 20 min) as compared with pancuronium (1.8 ± 0.4 ml·kg⁻¹·min⁻¹; 140 ± 25 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_{ss} 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_{ss} (50))

VECURONIUM (ORG NC45, Norcuron™) is a mono-quaternary 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.

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 μg/kg) or vecuronium (n = 5, 25–50 μg/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 infusion[3] 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 ± 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_{ss}^{50} (ng/ml)
Pancuronium	4	2.7 ± 1.2	20 ± 9	140 ± 25	0.05 ± .02	0.26 ± .07	1.8 ± 0.4	88 ± 34
Vecuronium	5	2.2 ± 1.4	13 ± 8	71* ± 20	0.05 ± .02	0.27 ± .04	5.2* ± 0.7	94 ± 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 ($Cp_{ss}50$). 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 $Cp_{ss}50$ (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
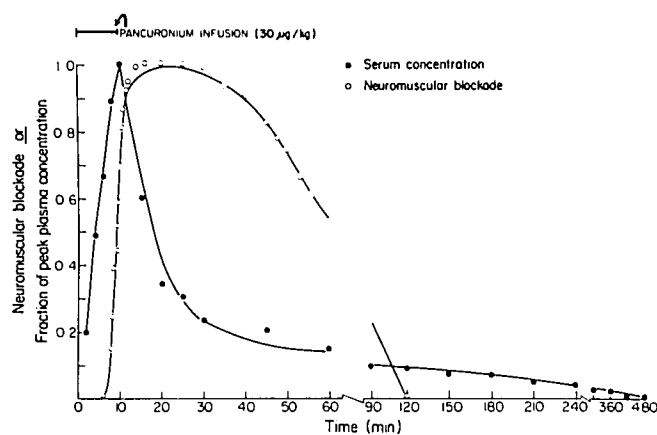

FIG. 1. Data from a patient anesthetized with halothane in whom pancuronium was infused over a 10-minute period. Plasma concentration is plotted as the fraction of the peak plasma concentration observed. Neuromuscular blockade is plotted from 0 = no paralysis to 1 = 100% paralysis. The solid lines represent 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.
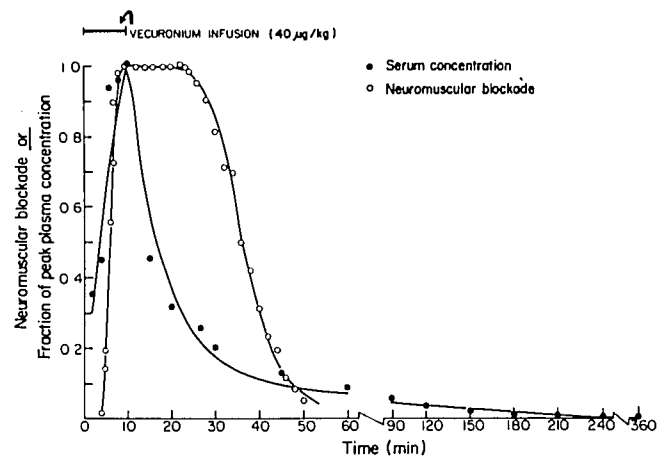

FIG. 2. Data from a patient anesthetized with halothane in whom vecuronium was infused over a 10-minute period. Plasma concentration is plotted as the fraction of the peak plasma concentration observed. Neuromuscular blockade is plotted from 0 = no paralysis to 1 = 100% paralysis. The solid lines represent 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 monoquaternary compound and more lipid-soluble than pancuronium, the steady-state distribution volumes (Vd_{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 animals[13] 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 $Cp_{ss}50$ 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.

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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_0 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.