

Pancuronium and Vecuronium Pharmacokinetics and Pharmacodynamics in Younger and Elderly Adults

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To evaluate the effect of aging on the distribution, metabolism, and neuromuscular junction sensitivity to pancuronium and vecuronium, the authors determined the pharmacokinetics and pharmacodynamics of these drugs in 12 healthy elderly subjects (70-84 yr) and 12 young adults (30-57 yr) during halothane-nitrous oxide anesthesia. Plasma concentrations of the muscle relaxants were determined using a selective ion-monitoring mass spectrometric technique specific for the parent compound. For vecuronium, plasma clearance (3.7 ± 1.0 and 5.2 ± 0.8 ml · kg⁻¹ · min⁻¹, respectively), and volume of distribution at steady-state (179 ± 31 and 244 ± 38 ml · kg⁻¹, respectively) were lower in the elderly than in young adults; values for distribution half-lives, elimination half-life, and sensitivity of the neuromuscular junction were similar for the two groups. For pancuronium, there were no statistically significant differences between groups for these pharmacokinetic or pharmacodynamic parameters. However, there was a trend toward reduced clearance (20%) and prolonged elimination half-life (16%) in the elderly as compared to the younger patients. The authors conclude that healthy elective surgical patients between the ages of 70 and 84 yr of age do not differ markedly from younger adults in their pharmacokinetic/pharmacodynamic response to vecuronium and pancuronium. (Key words: Age factors. Neuromuscular relaxants: pancuronium; vecuronium. Pharmacodynamics: Cp₁₅₀. Pharmacokinetics: kinetics; models.)

PANCURONIUM,¹ D-TUBOCURARINE,² AND METOCURINE² have a prolonged duration of action in elderly patients. This prolonged action could be due to age-related changes in distribution, metabolism, elimination of these drugs, and/or age-related changes in the sensitivity of the neuromuscular junction. Two studies^{1,3} demonstrated reduced plasma clearance of pancuronium resulting in prolonged elimination half-life. A third study⁴ showed no age-related change in pancuronium clearance. Duvaldestin *et al.*¹ found no change in neuromuscular sensitivity to pancuronium of elderly patients as compared to younger patients. However, all three studies^{1,3,4} used a spectrofluorimetric analytic tech-

nique,⁵ which cannot distinguish between the parent compound and its metabolites. Because the metabolites of pancuronium have some neuromuscular blocking activity,⁶ the contribution of metabolites to prolonged elimination half-life and prolonged duration from pancuronium administration could not be estimated by these investigators.^{1,3,4}

Indirect evidence suggests that there may be age-related alterations in the pharmacokinetics and/or pharmacodynamics of vecuronium. d'Hollander *et al.*⁷ reported reduced steady-state dose requirement and increased recovery time (time for twitch tension to recover from 25-75% of control tension) after steady-state infusion of vecuronium in patients 60 yr or older compared to younger adults. A reduction in steady-state dose requirement in the older patients could be attributed to either reduced plasma clearance or increased sensitivity of the neuromuscular junction, and the prolonged recovery time to reduced plasma clearance or increased steady-state volume of distribution compared to younger patients. However, these variables were not measured by d'Hollander *et al.*⁷ Accordingly, to clarify age-related changes in responses to both pancuronium and vecuronium, we compared the pharmacokinetics and pharmacodynamics of both drugs in elderly patients and younger adults, analyzing plasma drug concentrations with a mass spectrometric technique specific for the parent compound of both drugs.

Methods

After receiving approval from our local committee on human research, and informed consent, we studied 12 young adult patients (ages ranging from 30-57 yr) and 12 elderly patients (ages ranging from 70-84 yr) ASA PS I or II undergoing elective surgery. All patients were chosen to insure absence of any historical or laboratory evidence of renal, hepatic, or neuromuscular disease. All patients had normal values for serum electrolytes, creatinine, blood urea nitrogen, serum glutamic oxaloacetic transaminase, lactic acid dehydrogenase, and alkaline phosphatase. Surgical procedures were all gynecologic, urologic, otorhinolaryngologic, or peripheral extremity surgery, involving minimal blood loss. Patients were given no medication known to alter response to muscle relaxants. Other demographic information is listed in table 1.

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TABLE 1. Ages (Yr) and Respective Weights (kg) of Patients

	VECURONIUM				PANCURONIUM			
	Younger		Elderly		Younger		Elderly	
	Age	Weight	Age	Weight	Age	Weight	Age	Weight
	30	63	70	78	32	77	70	65
	33	70	72	67	34	58	71	87
	39	45	76	80	35	64	73	77
	39	62	79	62	44	79	73	74
	40	66	80	50	46	54	77	64
			84	56	54	65	79	67
					57	63		
Mean ± S.D.	36 ± 4	61 ± 10	77 ± 5	66 ± 12	43 ± 10	66 ± 9	73 ± 3	72 ± 9

Patients were not premedicated. Anesthesia was induced with thiopental, 2–4 mg · kg⁻¹ iv, and halothane in 60% nitrous oxide, *via* a face mask. Concentrations of delivered anesthetic gases were measured continuously by mass spectrometry. The end-tidal concentration of halothane was age-adjusted to 75–85% of minimum alveolar concentration (MAC),^{8,9} (0.6–0.7% for young and 0.5% for elderly adults). Following induction of anesthesia, the trachea was sprayed with 4 ml of 4% lidocaine and intubated without the use of muscle relaxants. Ventilation was controlled to maintain end-tidal P_{CO₂} between 30 and 40 mmHg. Esophageal temperature was maintained above 35.5° C by the use of iv fluid warmers, warming blankets, and humidified ventilation.

A Grass S-44 stimulator delivered supramaximal square-wave bipolar 0.15 Hz impulses of 0.15-ms duration to thin-walled 27-gauge steel-needle electrodes placed subcutaneously, 3 cm apart, near the ulnar nerve at the wrist. The resultant force-of-thumb adduction was measured by a Grass FT-10 force-displacement transducer and recorded continuously on a polygraph. After 30 min of stable end-tidal halothane concentration, pancuronium or vecuronium was infused at a rate of approximately 2.5 μg · kg⁻¹ · min⁻¹. The infusion was continued until twitch tension had decreased to 30–20% of control twitch tension (7–16 min). The infusion was then terminated. Venous blood samples (3 ml each) were taken from the patient's contralateral arm before infusion and at 2, 4, 6, 8, 10, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360 min after the infusion began. Selective ion-monitoring mass spectrometry was used to measure the plasma drug concentrations of both pancuronium and vecuronium.¹⁰ This assay was sensitive to 2 ng · ml⁻¹ and measured only unmetabolized parent compound; coefficient of variation was 5–9.5% in the concentration range 2–20

ng · ml⁻¹ and 1.5–3.2% in the concentration range of 25–500 ng · ml⁻¹. Plasma concentrations were fitted to both 2- and 3-compartment pharmacokinetic models modified for an infusion¹¹ using a non-linear least squares regression analysis. A 3-compartment model was selected for all patient groups using the method of Boxenbaum *et al.*¹² Pharmacokinetic parameters were determined using standard formulas: rapid distribution half-life ($t_{1/2\pi}$), distribution half-life ($t_{1/2\alpha}$), elimination half-life ($t_{1/2\beta}$), volume of the central compartment (V_1), volume of distribution at steady-state ($V_{d_{ss}}$), and clearance (Cl).¹³

The magnitude of neuromuscular blockade was fitted to the estimates of the pharmacokinetic parameters using the method of Sheiner *et al.*¹⁴ This allowed determination of the pharmacodynamic parameters: the steady-state plasma concentration producing 50% depression of twitch tension (Cp_{ss50}); the term that describes sigmoidicity of the fitted function (γ); and the rate of equilibration of the muscle relaxant between the plasma and the site of action (k_{eo}). Mean values for the pharmacokinetic and pharmacodynamic parameters were compared between elderly and respective younger adult groups by the Student's *t* test for unpaired data.¹⁵ Differences were considered significant when $P < 0.05$.

Data from four of the five younger adults given vecuronium and four of the seven younger adult patients given pancuronium have been reported previously.¹⁶

Results

The $V_{d_{ss}}$ and Cl of vecuronium in elderly patients were approximately 30% less than in the younger adults (table 2) ($P < 0.05$). However, the $t_{1/2\pi}$, $t_{1/2\alpha}$, and $t_{1/2\beta}$ were similar for both age groups. Pharmacodynamic parameters Cp_{ss50} , k_{eo} , and γ were similar for both age groups (table 2).

With pancuronium, there were no significant differences between groups in any of the pharmacokinetic or pharmacodynamic parameters (table 3).

Discussion

The pharmacokinetics and pharmacodynamics of neuromuscular blocking drugs could be altered by increasing age, *per se*, and/or age-related diseases. We were meticulous in attempting to select elderly patients who did not have overt diseases commonly associated with elderly patients (see Methods for details). Furthermore, we carefully selected surgical procedures which should not alter the pharmacokinetics of vecuronium or pancuronium. Other than a slight reduction in Cl and $V_{d_{ss}}$ with vecuronium, we, therefore, conclude that increasing age, *per se* (i.e., ages 70–84 yr), does not appreciably alter the pharmacokinetics and pharmacodynamics of vecuronium or pancuronium. We can only speculate that the other investigators, who did find age-related changes,^{1,3,7} utilized a less stringent process in selecting elderly patients to study.

That vecuronium, and not pancuronium, was associated with an approximate 30% decrease in Cl and $V_{d_{ss}}$ may be related to their difference in route of elimination. Pancuronium is primarily eliminated *via* the kidney, whereas vecuronium is primarily eliminated into the bile.^{17,18} That vecuronium and pancuronium have such similar structures, but such different pharmacokinetics, has not been explained. However, our results suggest that drugs dependent on biliary excretion will be influenced more by increasing age than those drugs dependent on the kidney for their elimination.¹⁹

Our results contrast with those of d'Hollander *et al.*,⁷ who did not perform a pharmacokinetic study of vecuronium. However, their study had pharmacokinetic implications. They determined steady-state dose requirement (SSDR) and time for twitch tension to recover from 25–75% of control (TH_{25-75}) after steady-state infusion in three age groups: less than 40 yr, 40–60 yr, and greater than 60 yr. SSDR was reduced 34% and TH_{25-75} increased over 100% in the group aged 60 yr or older. Applying a pharmacokinetic/pharmacodynamic perspective, the reduced SSDR in the elderly could be attributed to enhanced neuromuscular sensitivity and/or a reduced Cl. The first possibility appears unlikely. Our study of vecuronium and pancuronium and other studies of pancuronium,¹ d-tubocurarine, and metocurine² have demonstrated no significant difference between elderly and younger patients in neuromuscular junction sensitivity to nondepolarizing neuromuscular blocking drugs. An argument could be made

TABLE 2. Vecuronium Pharmacokinetic and Pharmacodynamic Values (Mean \pm SD) in Elderly and Younger Adults

n	Elderly (6)	Younger Adults (5)
$t_{1/2\pi}$ (min)	1 \pm 1	2 \pm 2
$t_{1/2\alpha}$ (min)	9 \pm 3	15 \pm 6
$t_{1/2\beta}$ (min)	58 \pm 10	70 \pm 20
V_1 (ml \cdot kg ⁻¹)	29 \pm 22	52 \pm 26
$V_{d_{ss}}$ (ml \cdot kg ⁻¹)	179 \pm 31*	244 \pm 38
Cl (ml \cdot kg ⁻¹ \cdot min ⁻¹)	3.7 \pm 1.0*	5.2 \pm 0.8
k_{eo} (min ⁻¹)	0.165 \pm 0.052	0.169 \pm 0.021
Cp_{ss50} (ng \cdot ml ⁻¹)	106 \pm 21	92 \pm 37
γ	4.84 \pm 1.17	5.80 \pm 0.95

* Different from younger adults $P < 0.05$ by Student's *t* test for unpaired data.

that we compared Cp_{ss50} values, while d'Hollander *et al.*⁷ indirectly evaluated Cp_{ss90} values. If the plasma concentration *versus* percent paralysis relationship between the elderly and younger patients is not parallel, then this could explain the discrepancy between the two studies. However, available evidence suggests that the plasma concentrations *versus* percent paralysis relationships for nondepolarizing drugs is parallel between elderly and younger patient populations.^{1,2} The second possibility, reduced Cl without a change in neuromuscular junction sensitivity, perhaps provides a better explanation for the reduced SSDR in the elderly found in the d'Hollander *et al.* study.⁷ This explanation is consistent with the findings of the current study.

The d'Hollander *et al.*⁷ finding that TH_{25-75} for vecuronium increased 100% in the elderly is more difficult to reconcile with our data. After an infusion approaches steady-state, the recovery of neuromuscular blockade is predominantly dependent on $t_{1/2\beta}$ (which is, in turn, dependent on both Cl and $V_{d_{ss}}$). Therefore, if steady-state had been achieved by d'Hollander *et al.*,⁷ this suggests that $t_{1/2\beta}$ was prolonged in their elderly

TABLE 3. Pancuronium Pharmacokinetic and Pharmacodynamic Values (Mean \pm SD) in Elderly and Younger Adults

n	Elderly (6)	Younger Adults (7)
$t_{1/2\pi}$ (min)	3 \pm 2	3 \pm 2
$t_{1/2\alpha}$ (min)	21 \pm 18	16 \pm 9
$t_{1/2\beta}$ (min)	151 \pm 57	130 \pm 37
V_1 (ml \cdot kg ⁻¹)	57 \pm 36	43 \pm 21
$V_{d_{ss}}$ (ml \cdot kg ⁻¹)	218 \pm 37	212 \pm 79
Cl (ml \cdot kg ⁻¹ \cdot min ⁻¹)	1.2 \pm 0.3	1.5 \pm 0.5
k_{eo} (min ⁻¹)	0.135 \pm 0.073	0.173 \pm 0.075
Cp_{ss50} (ng \cdot ml ⁻¹)	123 \pm 29	107 \pm 35
γ	4.86 \pm 1.02	4.77 \pm 0.97

There were no significant differences between groups ($P < 0.05$).

subjects. In contrast, we measured $t_{1/2\beta}$ and found that it was similar for elderly and younger patients. Because Cl appears to be reduced in both studies, the only explanation for these differing results is that $V_{d_{ss}}$ was reduced in the elderly *versus* younger population in our study, while $V_{d_{ss}}$ was unchanged for the two groups in the d'Hollander *et al.* study.⁷ Possible explanations for this difference include: 1) a difference in anesthetic technique (nitrous oxide-halothane in our study *versus* nitrous oxide-fentanyl in the d'Hollander *et al.* study); 2) a younger elderly population in the d'Hollander *et al.* study (age > 60 yr *versus* age > 70 yr) resulting in less reduced $V_{d_{ss}}$ due to less age-related reduction of muscle mass, total body water, and blood volume; 3) a healthier elderly population in our study; and 4) differences in surgical blood loss. We cannot ascertain which of these factors was responsible for the differences between our study and that of d'Hollander *et al.*⁷

Our pancuronium data, unlike those of Duvaldestin *et al.*¹ and McLeod *et al.*,³ did not reveal significant changes in pancuronium Cl in elderly and younger patients. However, though not statistically significant, the data were trending in the direction found by these previous investigators. For example, the mean values for Cl and $t_{1/2\beta}$ were decreased 20% and increased 16%, respectively, for elderly patients as compared to younger patients. Again, we believe we were unable to detect larger differences between the age groups because the elderly receiving pancuronium in our study were healthy individuals. There was no evidence of renal or hepatic disease, and ages ranged from 70–79 yr. Thus, our elderly patients were younger (and perhaps healthier) than those studied by Duvaldestin *et al.*¹ (n = 28, age 75 yr and older). Alternatively, it is possible that the trends we found (decreased Cl and increased $t_{1/2\beta}$ in the elderly as compared to younger adults) represent real differences between the groups but are not significant by our statistical analysis. Due to the variability of the pharmacokinetic data, it would require much larger numbers of patients to yield statistical significance if the means and standard deviations for these data did not change. We consider the variability of our pharmacokinetic data to be typical of the neuromuscular blocking drugs.

Our findings for pancuronium distribution volume ($V_{d_{ss}}$ in this study) agree with data from previous investigations indicating no significant difference between age groups for $V_{d_{ss}}$ ³ or V_{β} .^{1,3} Consequently, if the duration of action for pancuronium is prolonged in a given elderly patient, it is more likely due to reduced clearance of the drug than to a change in volume of distribution.

Perhaps the prolonged duration of action of pancuronium in elderly *versus* younger patients is the result of delayed elimination of potent metabolites (e.g., 3-OH-pancuronium has one-half the potency of the parent compound).⁶ If this were true, our calculated Cp_{ss50} for the parent compound would have been less in the elderly than the younger patients. This was not our finding (table 3). The fact that the kinetic values we derived for pancuronium in younger patients using techniques specific for the parent compound are remarkably similar to data from nonspecific fluorimetric assays^{1,3,4} suggests that the contribution of metabolites to fluorimetrically measured levels of pancuronium was insignificant.

We conclude that, in healthy elderly patients (between the ages of 70 and 84 yr) undergoing elective surgery, the elimination half-life of and sensitivity of the neuromuscular junction to vecuronium and pancuronium are not significantly different than those in younger adults. Cl and $V_{d_{ss}}$ are slightly decreased (30%) for vecuronium. Healthy elderly patients in this age group do not appear to represent a population distinctly different from younger adults in the pharmacokinetic/pharmacodynamic response to these drugs. However, the aging process includes a progressive decline in renal and hepatic elimination mechanisms,¹⁹ which, at the extremes of old age (*i.e.*, older than 70–84 yr), or in the presence of progressive illness, may result in reduced clearance and prolonged duration of action of pancuronium and vecuronium.

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