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Pharmacokinetics, Pharmacodynamics, and Dose–Response Relationships of Pancuronium in Control and Elderly Subjects

P. Duvaldestin, M.D., J. Saada, M.D.,† J. L. Berger, M.D.,‡ A. D'Hollander, M.D.,§ J. M. Desmonts, M.D.¶*

Twenty-eight elderly patients (>75 years old) and 43 younger patients (25 to 60 years old) were studied to evaluate the effect of aging on the pharmacokinetics and pharmacodynamics of pancuronium. The pancuronium dose–response relationship and the duration of neuromuscular blockade after the administration of a single dose (70 to 100 μg/kg) were compared in the two groups. The plasma concentration–response relationship was established during recovery from paralysis. The pharmacokinetics of pancuronium were characterized after a single bolus dose by measuring plasma and urine concentrations of pancuronium fluorimetrically. The dose–response and plasma concentration–response relationships in elderly patients were comparable to that of the control group. The dose that caused 50 per cent paralysis averaged 39 ± 10 and 44 ± 12 μg/kg in control subjects and elderly patients, respectively. The plasma concentrations corresponding to a fixed degree of neuromuscular blockade were similar between the two groups. The time for recovery of the twitch tension to 25 per cent of the control value was prolonged from 44 ± 10 to 73 ± 22 min in the elderly patients. The recovery rate of the twitch from 25 to 75 per cent of the control value also was prolonged from 39 ± 13 to 62 ± 30 min in the elderly patients. The plasma clearance was decreased by 35 per cent in the elderly patients and caused a prolongation of the elimination half-life to 201 min as compared with 107 min in the younger adults. Urinary excretion of pancuronium was delayed in the elderly patients. It is concluded that pancuronium exerts a prolonged effect in elderly patients because of delayed elimination; the pharmacodynamics of pancuronium are not altered by aging. (Key words: Age factors. Neuromuscular relaxants: pancuronium. Pharmacodynamics: ED_{50}. Pharmacokinetics.)

THE RESPONSE TO PANCURONIUM may be different in elderly patients and in younger patients for several reasons. First, muscle atrophy is often present in aged patients[1] and may cause muscular weakness; therefore aged patients may be more sensitive to muscle relaxants. Second, the reduced extracellular fluid space in elderly[2] persons may decrease the volume of distribution of hydrophilic compounds like pancuronium. Third, an age-related decrease in the glomerular filtration rate[3] may slow down the rate of elimination of pancuronium. These latter two factors may result in higher blood levels of pancuronium in elderly individuals as compared with their younger counterparts.

Conflicting results have been reported concerning the elimination of pancuronium in elderly patients. The originally observed decrease in the rate of plasma clearance of pancuronium with aging[4] was not confirmed in a more recent study.[5] However, an increase in the elimination half-life of pancuronium was found in older patients treated with pancuronium for severe tetanus.[6] In this report, we compare the pharmacodynamics and pharmacokinetics of pancuronium in aged and middle aged patients.

Methods

Adult patients requiring surgery under general anesthesia were studied after informed consent had been obtained. The protocol for this study was approved by the Human Studies Committee of the University of Paris 7. Two age groups were selected. The control group consisted of 43 patients whose ages ranged from 25 to 60 years, the older age group consisted of 28 patients older than 75 years. None of the patients had renal or liver diseases.

Approximately one hour before anesthesia, all patients received 0.5 mg intramuscular atropine and 5–15 mg droperidol. Anesthesia was then induced by the intravenous administration of 4–6 mg/kg thiopental and 2.5–4 μg/kg fentanyl, or 25–50 μg/kg phenoperidine. Endotracheal intubation was performed after application of 3 ml lidocaine 5 per cent to the larynx. Anesthesia was maintained with 60 per cent nitrous oxide and repeated doses of fentanyl or phenoperidine. Ventilation was controlled. Esophageal body temperature was monitored in all patients and never fell below 36° C. In long abdominal operations, body temperature was maintained with the aid of a warming mattress.

In the first part of the study, the pharmacodynamics of pancuronium were compared in the two age groups. A Grass S-48 stimulator was used to administer supramaximal single stimuli of 0.2- ms duration at a rate of 0.1 Hz to the ulnar nerve at the wrist through thin-wall needle electrodes. The evoked response of the adductor pollicis, *i.e.*, the twitch height (TH) was quantitated continuously with a Statham UC3 force transducer and recorded on a polygraph. Cumulated log dose–response relationships were determined in 16 patients of the con-

* Associate Professor, Hôpital Bichat.
† Resident in Anesthesia, Hôpital Bichat.
‡ Assistant in Anesthesia, Hôpital Bichat.
§ Assistant in Anesthesia, Hôpital Brugmann.
¶ Professor and Head of Anesthesia, Hôpital Bichat.

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Address reprint requests to Dr. Duvaldestin: Departement d' Anesthésie, Hôpital Bichat, 46, rue Henri-Huchard, 75018, Paris, France.

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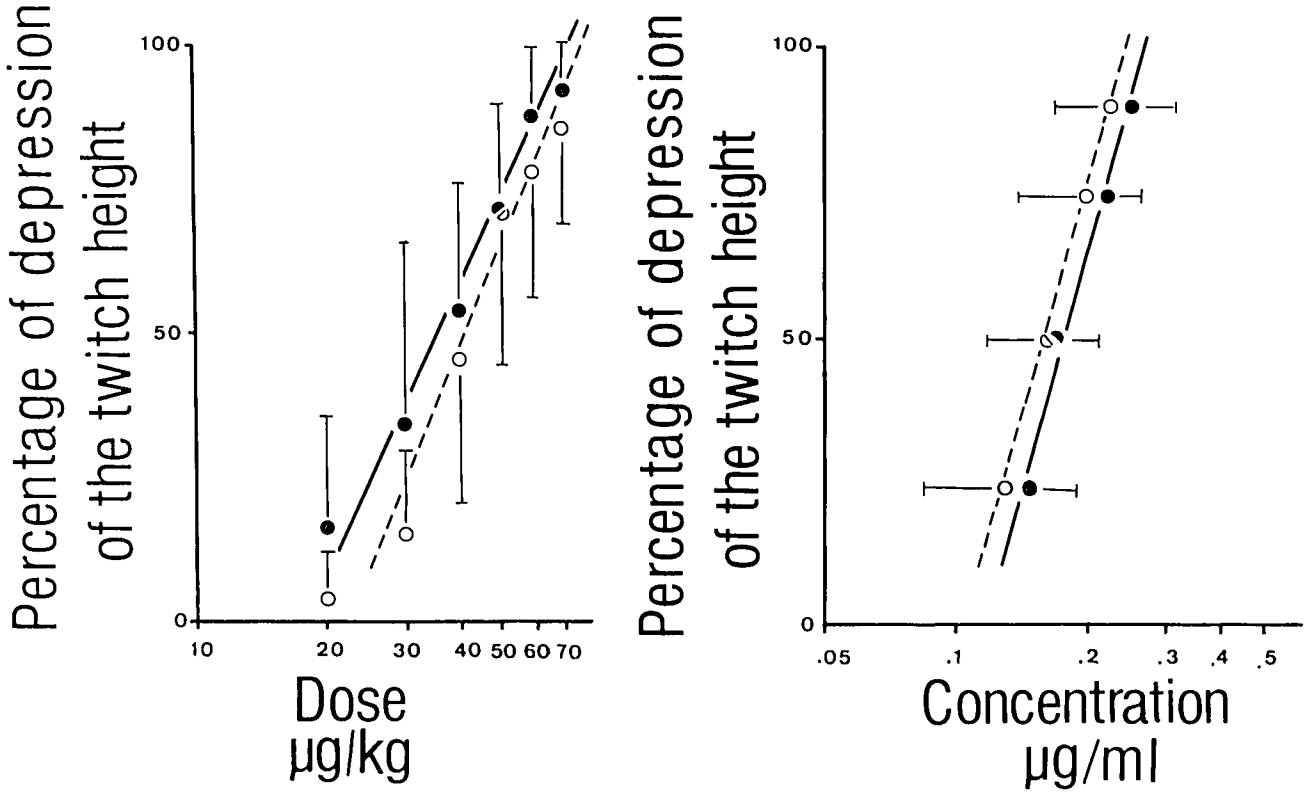

FIG. 1. Logarithmic plot of the mean (±SD) dosages and plasma concentrations against the paralytic effect in control patients (black circles) and elderly patients (white circles). The relationship between dosage and effect is established during the development of paralysis whereas the relationship between plasma concentration and effect is established during recovery from paralysis.

trol group (mean age ± SD: 43 ± 12 yr) and eight patients of the older age group (mean age: 81 ± 4 yr). A bolus dose of 20 µg/kg pancuronium was administered, followed by repeated doses as needed when the twitch response to the previous dose stabilized. Incremental doses were administered until 95 to 100 per cent paralysis was achieved. The total amount of pancuronium given for each response was plotted on a log dose–response graph from which linear regression was analyzed. From this curve, the dose of relaxant which caused 50 per cent TH depression (ED_{50}) was determined in each patient.

The speed of recovery from paralysis was estimated in 30 patients by measuring the intervals between several fixed degrees of neuromuscular blockade after the administration of pancuronium. For this part of the study, both patients who received a bolus dose only and those given repeated doses of pancuronium until a 95 to 100 per cent depression of the TH was achieved were included. Seventeen patients of the control group (mean age: 44 ± 11 yr) were studied. In nine of them, a bolus dose of 70 to 100 µg/kg was administered. Thirteen patients of the old age group (mean age: 81 ± 4 yr) were studied of whom five received a bolus dose. In all of these patients, blood samples were drawn every 30 min and at intervals corresponding to TH values of 5, 10, 25, 50, and 75 per cent during recovery from paralysis. The concentration corresponding to a TH of 50 per cent was defined as the Cp_{50}.

The relationships between the depression of the TH and the dose, and between the recovery of the TH and the plasma concentration were analyzed by a two-factor design. The first factors were the log of the cumulated dose and the log of the plasma concentration, respectively. The second factor in both studies was age. Each subject was studied repeatedly during the TH depression or the TH recovery and was analyzed accordingly. Linearity of the relationship between TH and log cumulated dose or plasma concentration was tested within the experimental design.[7]

In the second part of this investigation, the pharmacokinetics of pancuronium were studied in 15 older patients (mean age: 79 ± 4 yr) and in 18 patients of the control group (mean age: 35 ± 10 yr). Patients received a bolus dose of pancuronium, determined according to the expected duration of operation. The dose varied from 100 to 250 µg/kg in the control group and from 80 to 175 µg/kg in the older group. Serial blood samples were obtained from the fifth to the 360th min after pancuronium injection. When surgery required the insertion of a urinary catheter, urine samples were collected every

TABLE 1. Duration of Action of Pancuronium (min)

	Control Patients	Elderly Patients
Injection: 25 per cent twitch height	44 ± 10 (n = 17)	73 ± 22† (n = 13)
Injection: 75 per cent twitch height	83 ± 12 (n = 13)	137 ± 42* (n = 12)
Recovery: 10–75 per cent	55 ± 16 (n = 13)	87 ± 34* (n = 12)
Recovery: 25–75 per cent	39 ± 13 (n = 12)	62 ± 30* (n = 12)

* $P > 0.01$ *vs.* middle-age patients.
† $P > 0.001$ *vs.* middle-age patients.
Values are means ± SD.

2 h for the first 6 h and then 24 h after pancuronium administration. The total plasma or urine concentration of pancuronium and its metabolites was measured by a fluorimetric method.[8] The concentration of pancuronium was determined spectrofluorimetrically using a Jobin and Yvon spectrofluorimeter. Since this method does not discriminate between unchanged pancuronium and its bisquaternary metabolites, the total concentration was determined throughout. The lower limit of sensitivity of this method is 0.02 μg/ml. The accuracy (relative difference between actual and observed mean value in percentage) and precision (relative standard deviation in percentage) of the assay determined by tenfold processing of 200 ng pancuronium added to one ml human plasma were 1.5 per cent and 4 per cent, respectively. Plasma concentration profiles of pancuronium for each patient were fitted by a two-compartment open model. The equation describing the evolution of the plasma concentration (C) according to time (t) after the intravenous injection of pancuronium into a two-compartment open model is given by:

$$C = Ae^{-\alpha t} + Be^{-\beta t}.$$

The hybrid terms A and B and the hybrid rate constants α and β were calculated. The half-life of the elimination phase, the total apparent volume of distribution (AUC) measured according to the method of the area under the curve (Vd_{AUC}) and the plasma clearance (Cl) also were obtained. These variables were calculated by iterative fitting and computation procedures using the SAAM 25 program.[9] Statistical differences between the control group and the older group were analyzed by the two-tailed non-parametric Mann-Whitney U-test.[10]

Results

The dose–response relationship in the elderly was comparable to that observed in younger adults (fig. 1). The best fitting curve between the log cumulated dose of pancuronium *vs.* the percentage of TH depression was a straight line (fig. 1). The single main effect of age was not significant between the two groups. The mean (±SD) extrapolated dose corresponding to 50 per cent paralysis (ED_{50}) was not significantly different: 39(±10) and 44(±12) μg/kg in the control subjects and in the older age group, respectively. The cumulated doses that were necessary to achieve almost complete paralysis (*i.e.*, a TH height of less than 5 per cent) were similar in both groups: 78 ± 24 and 81 ± 26 μg/kg in the control and the older age group, respectively. No significant difference was observed between the two groups at any of the plasma concentrations corresponding to a fixed degree of paralysis (fig. 1). The plasma concentrations corresponding to 75 per cent depression of TH were 0.22 ± 0.05 and 0.20 ± 0.06 μg/ml in control subjects and elderly patients, respectively. The best fitting curve between the log plasma concentration of pancuronium *vs.* the percentage of TH depression was a straight line (fig. 1). The duration of action was estimated by the interval between the last injection of the cumulated dose or the injection of a bolus dose and the recovery to 25 or 75 per cent TH. In the elderly patients, the duration of action of pancuronium was significantly increased from injection till 25 per cent and 75 per cent TH recovery (table 1). The rate of recovery from 10 to 75 per cent TH or from 25 to 75 per cent TH also was prolonged in the elderly group. The main pharmacokinetic alteration observed in the elderly patients was a decreased plasma clearance from 1.81 ± 0.36 to 1.18 ± 0.39 $ml \cdot min^{-1} \cdot kg^{-1}$ whereas the total apparent volume of distribution (Vd_{AUC}) was not significantly modified (table 2). These pharmacokinetic alterations resulted in delayed plasma concentration decay (fig. 2) as was evidenced by the 100 per cent prolongation of the elimination half-life from 107 ± 24 to 201 ± 69 min. Urinary excretion of pancuronium was delayed in the elderly patients, which was most noticeable early after pancuronium administration (table 3).

Discussion

The results of the present study demonstrate in two different ways that pancuronium is as potent in elderly

TABLE 2. Pancuronium Pharmacokinetics (Mean ± SD)

	Control Patients (n = 18)	Elderly Patients (n = 15)
α (min^{-1})	0.0618 ± 0.0447	0.0613 ± 0.0326
β (min^{-1})	0.0065 ± 0.0015	0.0034 ± 0.0012*
A ($\mu g \cdot min^{-1}$)†	0.667 ± 0.336	0.534 ± 0.164
B ($\mu g \cdot ml^{-1}$)†	0.347 ± 0.095	0.325 ± 0.106
Vd_{AUC} ($ml \cdot kg^{-1}$)	275 ± 61	320 ± 102
Cl ($ml \cdot min^{-1} \cdot kg^{-1}$)	1.81 ± 0.36	1.18 ± 0.39*

* $P < 0.005$ *vs.* control patients.
† A and B were doses normalized for a single dose of 100 μg/kg.

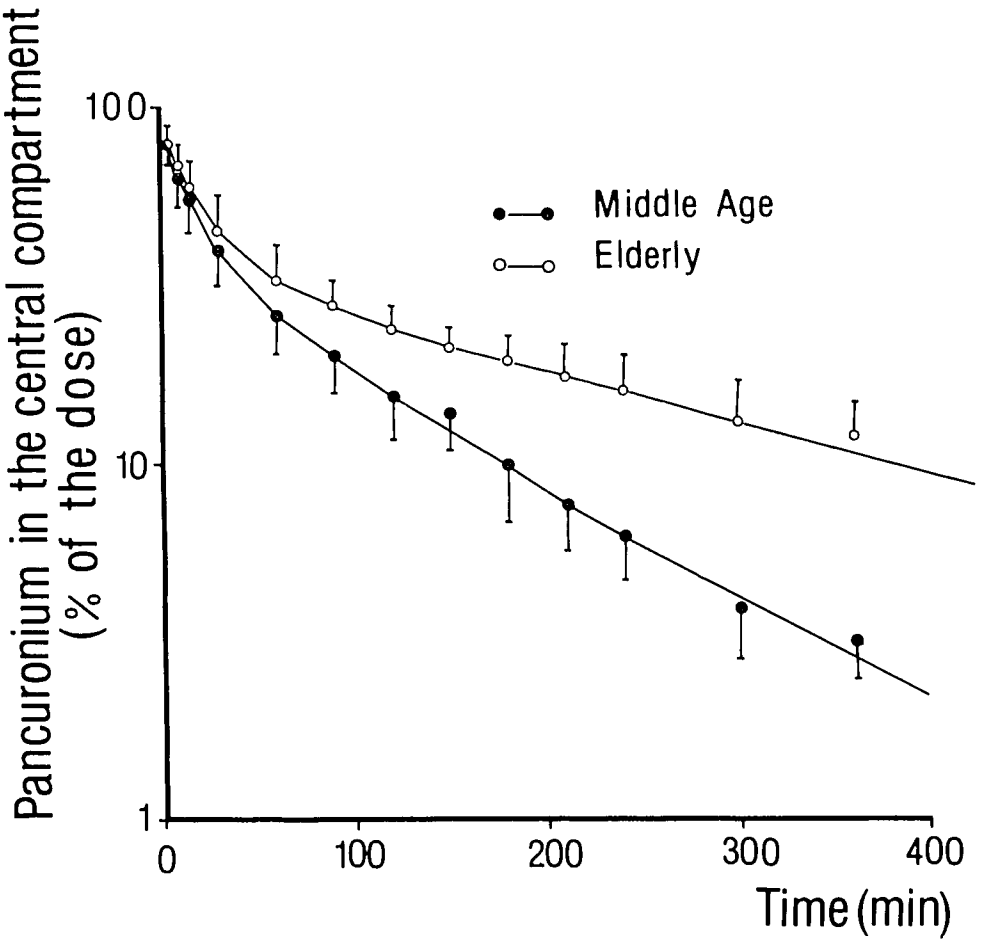

FIG. 2. Disappearance of pancuronium from the central compartment following a single intravenous injection. Semilogarithmic plot of the amount of pancuronium present in the central compartment (±SD) for control patients (black circles) and elderly patients (white circles).

individuals as in middle-age adults. The degree of paralysis obtained with similar doses was the same in both groups since the dose–response curves were comparable over the 25 to 95 per cent TH depression range (fig. 1). However, this study of potency on a whole-body basis provides only an estimation of the final effect without analyzing the events that occur between the injection of the drug and its action at the neuromuscular junction. This method does not take into account variations in the disposition of the drug and especially variations in the initial volume of distribution of the drug after an intravenous injection. Simultaneous measurement of the plasma concentration and the degree of paralysis eliminates this cause of error in the estimation of potency. Plasma levels also were found to be the same in the elderly group and in the control group. This finding suggests that the same concentration of pancuronium is present at the receptor site for the same effect regardless of the patient's age. Plasma concentrations were measured during recovery from paralysis at which time an equilibrium[11] or a pseudo-equilibrium[12] exists between the plasma and the area surrounding the motor endplate. When a relatively large dose of pancuronium is administered, such as a dose of 70 to 100 μg/kg in the present study, the period of recovery of the TH occurs during the elimination phase. The twitch height value of 25 per cent was achieved 44 and 73 min after pancuronium administration in the control and the elderly patients, respectively. At this time, the plasma concentration is mainly influenced by elimination processes and there is little or no difference in the concentration of pancuronium between the central compartment and the area surrounding the motor endplate. The influence of protein binding on the relationship between plasma concentra-

TABLE 3. Percentages of the Administered Dose of Pancuronium Recovered in the Urine (Mean ± SD) at Various times after Administration

	2 h	4 h	6 h	24 h
Control patients (n = 8)	35 ± 16	55 ± 17	57 ± 18	67 ± 18
Elderly patients (n = 6)	18 ± 9*	31 ± 9†	40 ± 13	47 ± 13

* $P < 0.05$ *vs.* middle-age patients.
† $P < 0.01$ *vs.* middle-age patients.

tion and effect can probably be ignored since pancuronium has been shown to be poorly bound to plasma proteins.[13]

The main difference in the response to pancuronium in elderly patients is a prolongation of the duration of action due to delayed elimination. The duration of action, which can be estimated by several methods, was defined as the interval between the last dose of pancuronium and the levels of TH determined during recovery from paralysis. The fact that repeated cumulated doses were administered instead of a bolus dose does not introduce an important change in the estimation of the duration of action. It has been previously shown for *d*-tubocurarine that the duration of effect was similar after small repeated doses or after a bolus dose.[14]

Alteration of pancuronium pharmacokinetics in elderly patients consisted mainly of decreased plasma clearance that resulted in a prolonged elimination half-life. Age had no influence on the distribution phase and the total apparent volume of distribution. The pharmacokinetic alterations reported in the present study agree with the findings of McLeod *et al.*[4] who also observed an age-related reduction of pancuronium clearance which they attributed to diminished renal function with advancing age. The reason why Somogyi found no significant change in pancuronium clearance according to age[5] may partly be explained by the small proportion of elderly subjects among the population examined since only a few subjects were older than 75 years and none older than 80 years. A decrease in renal excretion may account for the reduced plasma clearance of pancuronium. Pancuronium is normally excreted essentially unchanged through the kidneys by glomerular filtration. The drug is poorly bound to plasma proteins and tubular reabsorption appears unlikely since it remains completely ionized regardless of urinary *p*H. A decrease in urinary excretion of pancuronium can only be demonstrated early after its administration, whereas subsequently cumulated urinary excretion will appear normal in older patients. This slower rate of urinary excretion corresponds to the decreased glomerular filtration rate of the normal age kidney.[15] The contribution of a decline in hepatic uptake and biliary excretion of pancuronium in elderly patients may be an additional factor that was not investigated in the present study.

The increase in the elimination half-life of pancuronium will significantly increase the duration of action and especially the duration of recovery from paralysis. This prolongation of action was observed for relatively low doses of 80 μg/kg. The recovery time from 75 to 25 per cent of paralysis is measured at a time when the plasma decay is influenced mainly by excretion processes, thus the rate of recovery is linearly related to the elimination half-life.[11]

A model including both pharmacokinetics and pharmacodynamics was not proposed in the present study because these aspects could not be studied simultaneously in the same patient. However, agreement was observed between the two. The duration of action can be estimated from the averaged concentration corresponding to 75 or 25 per cent paralysis. The predicted values of the time between injection and recovery to 75 per cent twitch height were 65 and 120 min in the middle-age and old-age groups, respectively. These calculated values were relatively close to the mean observed values (table 1).

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