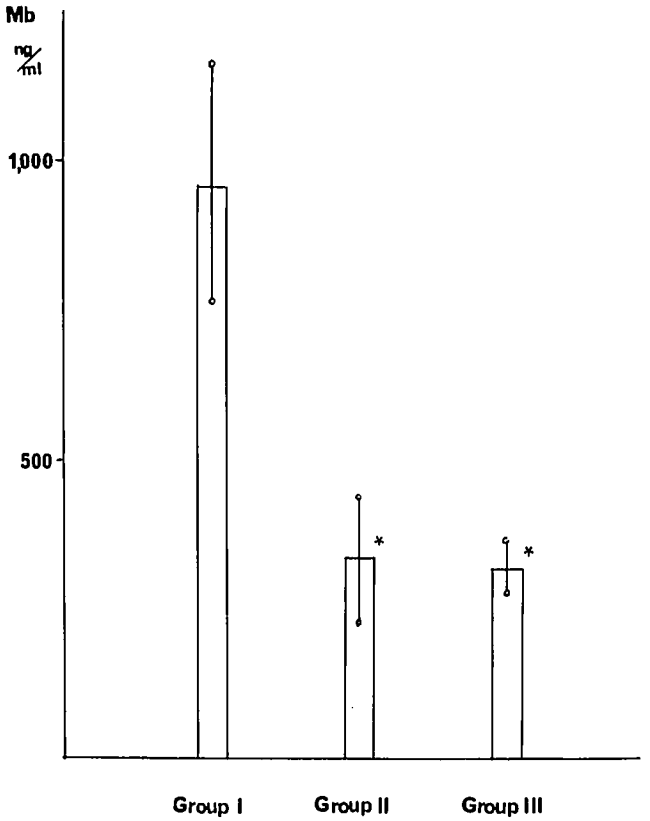

FIG. 1. Inhibitory effects of intravenous *d*Tc (Group 2) and oral dantrolene (Group 3) on halothane–SCh-induced elevation of serum Mb in comparison with the control (Group 1) (*$P < 0.05$).

supported by the work of Inagaki *et al.*,[6] whose elevated values of Mb in normal children under a similar situation were similar to ours.

A widely recommended method to diminish fasciculations and to alleviate muscle damage is pretreatment with a small dose of nondepolarizing muscle relaxant. Tammisto *et al.*[3] reported that 0.1 mg/kg of *d*Tc given iv prior to SCh administration reduced elevation of serum CPK activity induced by halothane and SCh. Our results in Group 2 confirm the efficacy of pretreatment with *d*Tc for halothane–SCh-induced myoglobinemia. Also, our results in Group 3 indicate that 2 mg/kg of orally administered dantrolene is as potent as 0.05 mg/kg of iv *d*Tc in decreasing serum levels of Mb induced by halothane and SCh. Further studies will be required to establish which is the preferred approach.

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Effect of Age and Premedication on Thiopental Sleep Dose

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The pharmacodynamics of thiopental in the elderly are not known. The available data[1–5] describe only the range or mean of "typical" thiopental dosages given to geriatric patients under various circumstances. Therefore, a clinical investigation was performed to define the thiopental sleep dose–effect relationship in geriatric surgical patients and to examine the role of both age and premedication in determining its characteristics.

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METHODS

Forty-one adults between the ages of 20 and 40 years and 102 patients 65 years or older were studied according to a protocol approved by the local Committee on Studies Involving Human Beings. Patients ASA physical status 1, 2, or 3 were selected arbitrarily from the elective sur-

TABLE 1. Demographics of Patient Groups (All Mean Values ± SEM)

	Young Adult Premedicated	Geriatric Unpremedicated	Geriatric Premedicated
n	41	40	62
Age (yrs), mean	29.1 ± 0.9	72.8 ± 1.0	71.6 ± 0.6
range	20–40	66–90	65–84
		$p < 0.001$	
Weight (kg), mean	68.6 ± 2.5	69.3 ± 2.2	69.6 ± 2.1
range	44–114	43–102	43–133
Male:female	13:28	24:16	30:32
Per cent patients admitting daily ethanol use	14.6	12.5	13.3
Per cent patients denying any ethanol use	29.3	47.5	45.0

gical schedule. No patient was studied if found to be acutely ill or have an intravascular volume deficit or if a clinical contraindication to thiopental existed. Patients also were excluded from the study on the basis of documented or presumed central nervous system disorders, cerebrovascular accident, or acute psychiatric disturbance.

At least 30 min prior to thiopental injection, each of the 41 premedicated young adult patients and 62 premedicated geriatric patients received morphine sulfate 5 to 10 mg im and atropine 0.2 to 0.4 mg im. An additional 40 geriatric patients received no medication for 8 h prior to surgery. All patients received 300–500 ml of physiologic crystalloid solution by iv infusion over a 20-min period immediately prior to administration of thiopental. Blood pressure was monitored by oscillotonometer and heart rate and rhythm by EKG and precordial stethoscope. Some patients had an arterial cannula inserted if clinically indicated. Age, weight, ethanol, and medication habits were obtained from nursing records and then confirmed by conversation with each patient.

A random number generator was used to select the dose of freshly prepared thiopental 2.5% (1.0–2.8 $mg \cdot kg^{-1}$ rounded to the next highest 5 mg, maximum dose 250 mg) for each patient. This dose was diluted to a final volume of 10 ml and injected iv over 5 s into a rapidly running infusion at the injection port closest to the patient. The time from completion of injection to loss of response to a verbal command ("open your eyes") and the time required for subsequent loss of the eyelash reflex, if applicable, were measured by stopwatch. Arterial blood pressure and heart rate were obtained immediately before and 90 s after thiopental injection. Final determination of loss of consciousness was made 90 s following completion of injection of the initial thiopental bolus.

Patients breathed oxygen via a face mask during thiopental injection, and no patient received any form of sedation or medication prior to thiopental injection other than the premedication described above. After determination of loss of consciousness, if any, induction of anesthesia proceeded as usual, with additional thiopental given at the discretion of the anesthetist responsible for clinical management of the patient. Typical clinical reasons justifying additional thiopental were the need to produce unconsciousness in the patients not demonstrating loss of consciousness with the initial thiopental bolus, persistent spontaneous movement or coughing, and attempts to blunt the cardiovascular response to laryngoscopy in patients demonstrating loss of consciousness after the initial thiopental bolus.

Dose–effect relationships for the various patient groups were constructed using a quantal dose–effect curve relating per cent of patients within each dosage group showing loss of consciousness to a logarithmic plot of thiopental dose expressed as $mg \cdot kg^{-1}$ total body weight using the probit method of Finney.[6] Statistical comparison of equivalent effective doses and mean vital signs were made using Student's t test, and chi-square analysis was used, where appropriate, to analyze demographic data. For all statistical techniques, the criterion of significance was $P < 0.05$.

RESULTS

The demographic comparisons of the three patient groups studied (geriatric premedicated, geriatric unpremedicated, and young adult premedicated) revealed no significant differences except age (table 1). The calculated median effective dose (ED_{50}) of thiopental required for loss of response to verbal command and abolition of the eyelash reflex for premedicated geriatric surgical patients (table 2) was 1.26 ± 0.16 $mg \cdot kg^{-1}$ (±SEM), significantly less ($P < 0.01$) than the corresponding value of 2.24 ± 0.09 $mg \cdot kg^{-1}$ obtained for similarly premedicated young patients. Thiopental ED_{50} for premedicated geriatric patients also was significantly less than the ED_{50} of 1.81 ± 0.11 $mg \cdot kg^{-1}$ calculated for their unpremedicated counterparts. ED_{90} values for geriatric premedicated, geriatric unpremedicated, and young adult premedicated patient groups rose progressively from 2.32 ± 0.41 to 2.45 ± 0.24 and 2.78 ± 0.20 $mg \cdot kg^{-1}$, respectively, but none of these differed significantly. The complete calculated dose–effect relationship for each of

the three groups with 95% confidence limits is presented in figure 1.

The mean time required for loss of the eyelash reflex in all geriatric patients studied was 48.1 ± 2.4 s, significantly longer than the 39.6 ± 2.8 s of the young patients; the range was 24 to 100 s in the elderly and 21 to 63 s in young patients. There were no significant differences in time to loss of response to verbal command between any of the three patients groups, and premedication of geriatric patients did not produce a significant alteration of the time required for loss of the eyelash reflex. Only two patients failed to respond to verbal command while maintaining active eyelash reflex within 90 s of thiopental injection. No patient lost the eyelash reflex without prior failure to respond to verbal command.

Systolic blood pressure 90 s after thiopental bolus infusion decreased significantly more in premedicated geriatric than in premedicated young adult patients, −9.7 ± 1.8 *versus* −3.8 ± 1.8 mmHg. Heart rate response to thiopental infusion was also significantly different: an increase of 5.2 ± 1.9 beats · min^{-1} occurred in the young adults, as compared with an increase of only 0.7 ± 0.8 beats · min^{-1} for geriatric patients. Premedication of geriatric patients did not alter the cardiovascular response to thiopental.

Discussion

Prior to this description of the thiopental sleep dose–effect relationship for geriatric surgical patients, recommendations for thiopental induction doses for the elderly ranged from 3.93 to 4.5 mg · kg^{-1}, with 5.4 to 6.0 mg · kg^{-1} reported for young adults.[3,5] The mean "minimum induction dose" in patients greater than 64 years has been described as 3.16 mg · kg^{-1}.[4] These thiopental doses and those of similar studies are considerably larger than the ED_{50} values obtained in this study, but they were determined by the use of a large initial thiopental bolus and additional increments injected at intervals as short as 15 s.[7] Thus, prior methods failed to allow for the prolonged time required for loss of consciousness in the elderly, a phenomenon clearly demonstrated in this study, and some studies permitted the injection of additional thiopental increments to accomplish more than simple loss of consciousness and elimination of the eyelash reflex. The mean total thiopental doses given to premedicated patients in the present study on clinical grounds were 3.69 ± 0.17 mg · kg^{-1} for the geriatric and 5.04 ± 0.25 mg · kg^{-1} for young adults, virtually the same as those described previously by others as "induction dosages."

Although of debatable clinical utility, ED_{50} is a classical index of anesthetic potency that makes possible comparisons of the median drug requirements of different patient groups without regard to variability in response within each group. ED_{50} values locate the midpoint of the dose–effect relationship on the horizontal log dose axis. The ED_{50} value for unpremedicated elderly patients obtained in the present study confirms that aging over the full range of lifespan appears to reduce significantly thiopental sleep–dose requirements: it is 17% less than the value reported previously in pharmacodynamic studies of unsedated young adults,[8] and 38% less than the ED_{50} values reported for unpremedicated children.[9] Premedication of the elderly is a significant factor as well, since the thiopental ED_{50} of elderly patients given light narcotic premedication in this study was 30% less than that of the group of unpremedicated but otherwise comparable ge-

TABLE 2. Incidence of Patients Showing Loss of Consciousness in Response to a Single iv Bolus Dose of Thiopental

Group	Thiopental Dose (mg · kg^{-1})	n	No. Patients Showing Loss of Consciousness
Geriatric, unpremedicated	1.0	10	0
	1.5	10	2
	2.0	10	7
	2.5	10	9
Geriatric, premedicated	1.1	10	4
	1.4	10	6
	1.6	11	7
	1.8	10	8
	2.0	10	8
	2.2	11	10
Young adult, premedicated	2.0	10	3
	2.2	11	4
	2.5	10	8
	2.8	10	9

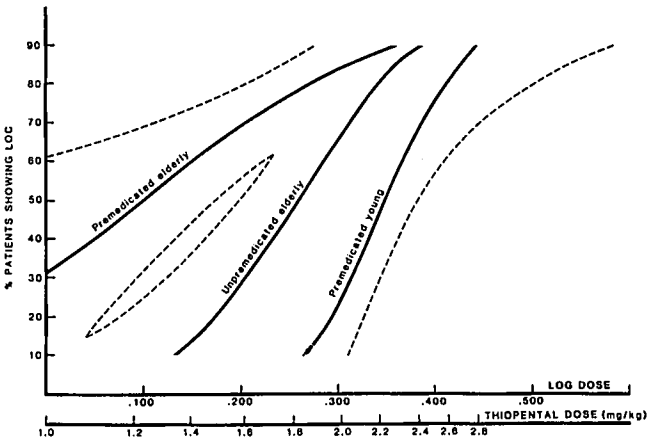

FIG. 1. Calculated dose–effect relationships for loss of consciousness (LOC) produced by iv thiopental in 40 unpremedicated elderly, 62 premedicated elderly, and 41 premedicated young adult surgical patients. Broken lines represent boundaries of 95% confidence limits. Chi-square values for the best-fit regression analysis of the three curves shown are 0.0896, 0.3951, and 0.6954, respectively, and r-values are 0.9946, 0.9748, and 0.9749.

riatric patients. There may not be a similar interaction between premedication and thiopental requirement in young adults: the ED_{50} value for premedicated young adults in this study is virtually identical to the value of 2.19 $mg \cdot kg^{-1}$ obtained by Stella *et al.* using comparable methods to study unsedated patients 20–50 years old.[8] Thus, in the context of anesthetic induction, as in other settings,[10] elderly patients appear to be more sensitive to the depressant effects of narcotic premedication than are young adults.

Calculated ED_{90} values provide a convenient estimate of the smallest thiopental dose required to produce predictable loss of consciousness, but they reflect both drug potency and variability and therefore have limited pharmacodynamic significance. In this study, the opposing factors of reduced drug requirement and increased variability for response to thiopental in elderly surgical patients combined to make the differences between the ED_{90} values of the three groups studied statistically insignificant. The slope of the dose–effect relationship for premedicated geriatric patients was, in fact, significantly reduced as compared with the slopes calculated for either of the other two patient groups ($P < 0.02$), confirming increased patient-to-patient variability. These data suggest that age and light narcotic premedication enhance thiopental potency and broaden the variability of response to thiopental.

This investigation did not study the mechanism for the reduction in thiopental ED_{50} and increase in variability of response seen in the elderly surgical patient, but the results cannot be explained by discrepancies in the demographics, since groups were matched for weight, sex, and patterns of ethanol use, and the two geriatric groups had the same distribution of physical status classifications. Burch and Stanski[11] have reported that protein binding, which may be reduced in the elderly, is not a significant factor in the early phases of thiopental distribution. Age-related decreases in circulating blood volume may increase the effective plasma concentration of thiopental following bolus infusion, but although analysis of plasma thiopental concentration may define initial-phase pharmacokinetics,[12] understanding thiopental pharmacodynamics in the elderly may require simultaneous determination of cerebrovascular and tissue thiopental concentrations to assess the effect of altered regional brain perfusion patterns, changes in neuronal function, or alteration in the effectiveness of the blood–brain barrier. Until this information is available, the role of physical status and organ system dysfunction in determining the response to thiopental in the patients in the present study needs further assessment. However, the increased time to loss of consciousness observed for elderly patients probably is a consequence of the well-documented decrease in cardiac index and prolongation of circulation time seen with advancing age.

Knowledge of thiopental pharmacodynamics in elderly patients assists in understanding the mechanics of anesthetic induction and provides an objective basis for adjustment of anesthetic induction sleep dose. In this clinical study, thiopental ED_{50} for loss of consciousness and abolition of the eyelash reflex in premedicated surgical patients 65 years or older was found to be 44% less than for a control group of comparably premedicated young adults. Both age and light morphine premedication appear to reduce the thiopental sleep dose requirements of elderly patients and increase the variability of thiopental response, making prediction of thiopental sleep dose more difficult in elderly than in young adult surgical patients.

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