

Thiopental Disposition as a Function of Age in Female Patients Undergoing Surgery

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The effect of age on the disposition kinetics of thiopental was studied in 22 lean female patients having a body mass index (weight (kg)/height(m)²) less than 30 and whose age ranged between 25 to 83 years. Patients underwent primarily abdominal surgery. A strong positive correlation between age and the apparent volumes of distribution, V_β and V_m , was found ($P < 0.001$). No significant relationship was found between total body clearance and age. The elimination half-life ($t_{1/2}$) of thiopental increased with age, and was primarily a function of volume of distribution. The free or unbound fraction of thiopental in serum (α) ranged between 0.168 and 0.276 and was significantly correlated with age ($P < 0.05$). Multiple regression analysis indicated that age was the independent variable which contributed most to the variability in $t_{1/2}$, V_β , and V_m . No conclusion can be reached concerning the potential differences in anesthetic induction doses required as a function of age; however, these data suggest that care may be required in the use of a balanced anesthetic technique in the elderly as a result of prolonged elimination. (Key words: Age factors. Anesthetics, intravenous: thiopental. Induction: anesthesia. Pharmacokinetics: thiopental.)

THE USE OF THIOPIENTAL in the elderly patient often engenders uncertainty regarding the appropriate dose and expected duration of action. The dose used is frequently different from that employed in younger patients but rarely is this alteration based on knowledge of the disposition kinetics of thiopental. Dundee¹ noticed that the anesthetic requirements of thiopental in humans were similar between 25 and 46 years of age. However, thiopental requirements were increased in patients under 25 years and decreased in those 46 years of age and over. A more recent study² investigated the effects of age, sex, serum creatinine concentration, and premedication on the size of the induction dose of thiopental in 540 patients. Thiopental induction doses were similar in the age groups below 60; however, an 18 per cent reduction in dose was found between 60 and 70 years of age, and a further 18 per cent reduction in dose was found be-

tween the ages of 70 and 80 years. The elderly represent an increasingly larger proportion of the population and there are more elderly candidates undergoing surgical procedures. It is important, therefore, to appreciate how aging may influence the disposition of thiopental. Such information may permit a more rational approach to dosing in the aged patient. The purpose of this investigation was to examine the disposition kinetics of thiopental as a function of age in women undergoing surgery.

Methods

Twenty-two lean, healthy adult female patients between the ages of 25 and 83 years, weighing 43.5 to 82.3 kg and undergoing elective, primarily abdominal surgery were studied. Body mass index (kg/m²) ranged between 15.7 and 28.4. A complete blood chemistry (SMA-20), urinalysis, hematocrit, and complete and differential blood counts were performed in each patient prior to the study. The study was approved by the Human Subjects Committee at the University of Arizona Health Sciences Center. Written consent to participate was obtained from each individual after the nature, purpose and risks of the investigation were explained.

In sixteen of the patients, premedication consisted of glycopyrrolate, 0.2–0.3 mg, im; diazepam, 10 to 15 mg, po, and/or morphine sulfate, 6–10 mg, im. Eighteen patients received gallamine (10–20 mg intravenously, iv) to prevent fasciculations. All patients were pre-oxygenated (three to five minutes) prior to induction of anesthesia. Anesthesia was induced with a predetermined dose of thiopental based on the judgement of the anesthesiologist (2.24–7.61 mg/kg). This was followed by succinylcholine administration (80–160 mg, iv) after loss of lid reflex and by placement of a cuffed endotracheal tube. Anesthesia was maintained (1.5 to 10.5 h) with a mixture of nitrous oxide, oxygen, and enflurane. Pancuronium bromide (1.33–10 mg, iv) was employed for muscle relaxation.

Ten ml arterial and/or venous blood samples were obtained prior to induction and at 5, 10, 15, 30, 45 min and at 1, 2, 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, and 96 h after induction of anesthesia with thiopental or until serum concentrations were less than 50 ng/ml. In some patients, blood samples were drawn from an arterial line for the first twenty-four hours. Thereafter, a heparin lock was used for all subsequent samples. In the other

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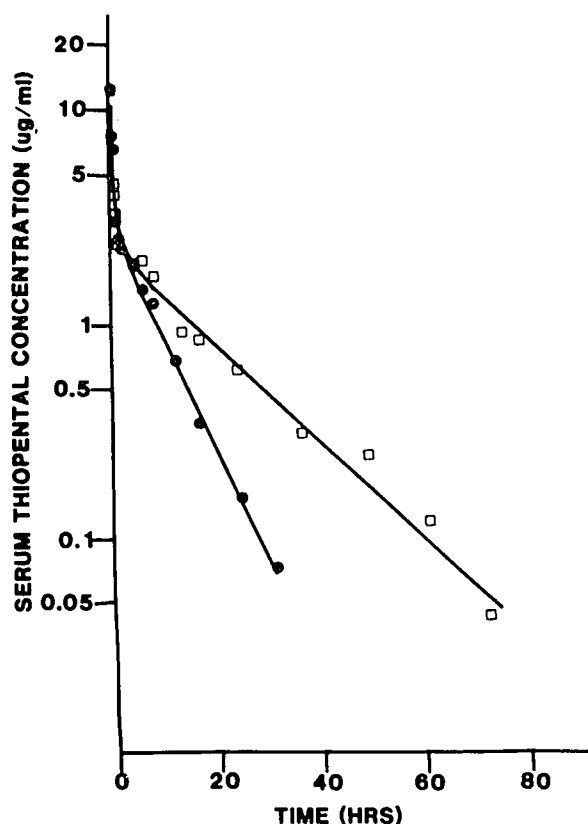


FIG. 1. Representative thiopental serum concentration-time curves for a young (29 years) and an elderly (77 years) patient after intravenous administration of sodium thiopental. The solid line represents a nonlinear regression fit of the data. ● = young patient; □ = elderly patient.

patients, all blood samples were drawn from a heparin lock. One hundred units of heparin were used to flush the heparin lock after a blood sample was obtained. Serum was obtained by centrifugation of the clotted blood samples within 60 min of drawing the sample and was kept frozen at -20°C .

All serum samples were assayed for thiopental using gas chromatography with a nitrogen-selective detector.³ The gas chromatographic procedure is sensitive to 25 ng/ml thiopental. Serum is acidified and extracted into hexane containing phenobarbital as the internal standard. The organic phase is back extracted into an aqueous alkaline solution which is then acidified and reextracted into hexane. Thiopental is derivatized *via* methylation and the derivatized thiopental and phenobarbital peaks are resolved completely having retention times of 1.7 and 1.3 min, respectively. The coefficients of variation at thiopental serum concentrations of about 0.05, 0.5, 1.0, and 10.0 $\mu\text{g/ml}$ are 6.0 per cent, 3.9 per cent, and 10.5 per cent and 3.5 per cent, respectively.

Other drugs commonly employed with thiopental (diazepam, fentanyl, morphine) do not interfere with the assay.

Zero time samples were spiked with 250 ng/ml ^{14}C -thiopental (6.3 m Ci/mmol, ICN, Isotope Nuclear Division, Irvine, CA) and equilibrium dialysis performed as previously described⁴ to determine serum protein binding.

The serum concentration (C) *vs.* time (t) data after intravenous administration of sodium thiopental were fit to the following equation:

$$C = \sum_{i=1}^n A_i \cdot e^{-\lambda_i \cdot t} \quad (1)$$

using the nonlinear least squares regression analysis program, NONLIN.⁵ In this equation n is the number of exponents required to describe the serum concentration-time data, A_i is a zero time intercept, and λ_i is a disposition rate constant. A weighting function of $1/C^2$ was found to provide the best fit of the data. Choice of an appropriate model was determined by use of an F-test.⁶ Initial estimates for A_i and λ_i required for input into NONLIN were obtained directly from a log C versus time plot using the method of residuals to resolve the curve into its various exponential components.⁷ Various pharmacokinetic parameters were calculated by conventional means.⁷ All results are expressed as mean \pm standard deviation.

The effect of age on the kinetic parameters for thiopental were determined by correlation analysis. A value of $P < 0.05$ was considered to be statistically significant. In addition, the simultaneous influence of several identifiable independent factors (age, smoking, status, alcohol use, serum protein concentration, serum albumin concentration, SGPT, SGOT, body mass index (BMI), and extent of protein binding [α]) on these kinetic parameters for total and unbound thiopental were determined by multiple linear regression analysis.⁸

Results

Serum creatinine, serum albumin, SGPT, and SGOT (except one patient) in the twenty-two patients were within normal limits. However, half of the patients in this study had serum protein concentrations slightly below normal (5.4 to 5.9 g/dl). The free fraction of thiopental (α) in serum was not related to serum thiopental concentrations. As noted previously⁴ heparin (*in vitro*) does not influence thiopental binding. Although the *in vivo* use of heparin has been implicated in altering drug plasma protein binding (*via* liberation of free fatty acids) to date only basic drugs have been shown to undergo this change.

Serum concentration versus time plots after intravenous administration of thiopental in a typical young and an elderly patient are presented in figure 1. The serum concentration-time data were best described by a linear two-compartment model in thirteen patients and by a three-compartment model in nine patients. The pharmacokinetic parameters of thiopental in each subject are available from the authors upon request.

The effect of age on the various pharmacokinetic parameters of thiopental are represented graphically in figures 2-5. A strong positive correlation between age and the apparent volumes of distribution, V_β and V_{ss} , was found. No relationship was found between age and volume of the central compartment (V_c). No significant relationship was found between total body clearance (Cl) and age. The relationship between age and the elimination half-life ($t_{1/2}$), which is a function of both the apparent volume of distribution and the systemic clearance, was found to be significant. The free fraction of

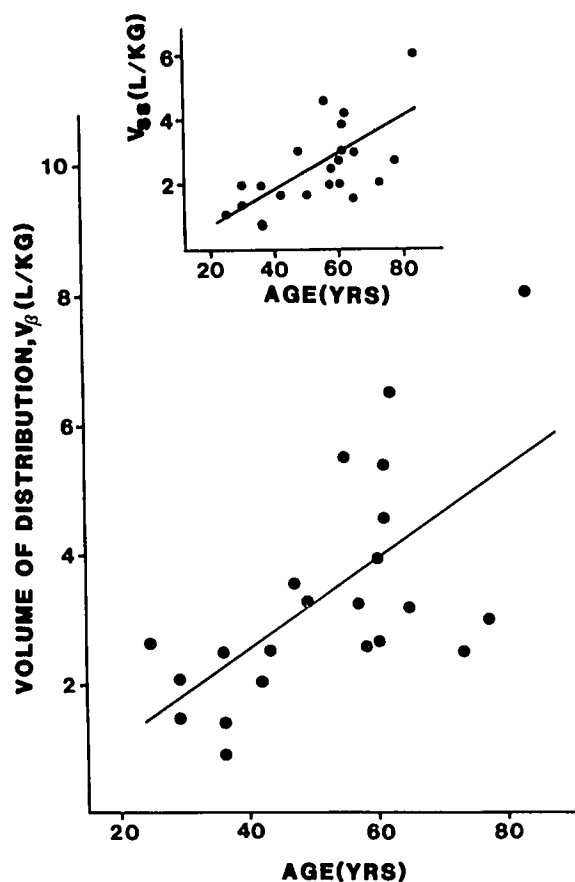


FIG. 2. Relationship between the volume of distribution (V_β) and the steady-state volume of distribution (V_{ss} , shown in the inset) of thiopental and age. The solid lines were determined by linear regression analysis (V_β : $r = 0.64$, $P < 0.001$; V_{ss} : $r = 0.70$, $P < 0.001$).

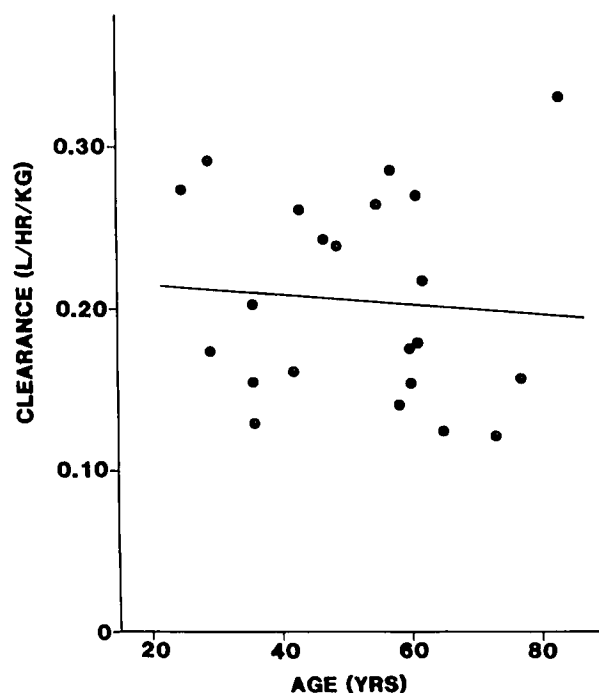


FIG. 3. Relationship between total body clearance (Cl) of thiopental and age. The solid line was determined by linear regression analysis ($r = -0.07$, $P > 0.05$).

thiopental (α), ranging from 0.168 and 0.276, correlated with age ($P < 0.05$). Because the increase in the apparent volumes of distribution for thiopental was much greater than the increase in free fraction of thiopental with increasing age, the apparent volumes of distribution based on unbound concentrations of thiopental, $V_{\beta u}$ and V_{ssu} , also exhibited a direct correlation with age. The apparent unbound clearance for thiopental tended to decrease with increasing age, suggesting an impaired ability of the liver to metabolize thiopental. However, the increase in the free fraction of thiopental with age was not large enough to significantly affect the relationship between age and the total body clearance of thiopental.

Multiple stepwise linear regression indicated that age was the independent variable accounting for the largest proportion of variability in free fraction, $t_{1/2}$, V_β , and V_{ss} . None of the independent variables tested significantly influenced the total body clearance of thiopental. Age was also the most important independent variable affecting the two apparent volumes of distribution based on unbound concentration, $V_{\beta u}$ and V_{ssu} .

Discussion

Previous studies that have examined the effect of age on thiopental dosage requirements have been inconclusive. A retrospective study¹ has determined that thiopental

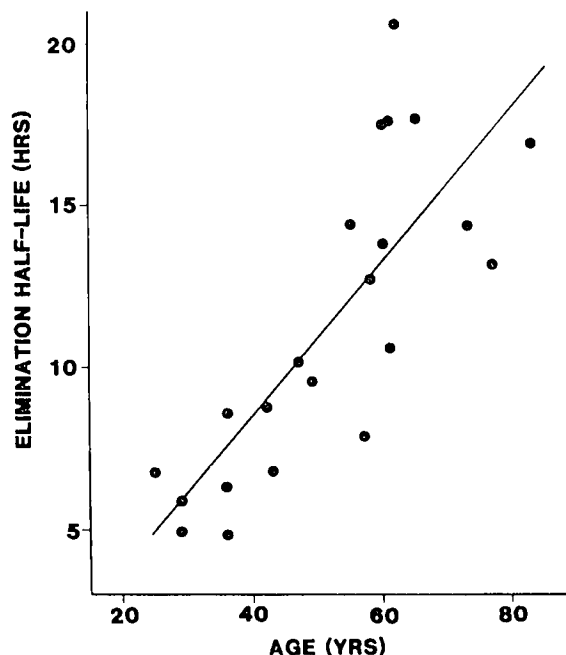


FIG. 4. Relationship between the elimination half-life ($t_{1/2}$) of thiopental and age. The solid line was determined by linear regression analysis ($r = 0.80$, $P < 0.001$).

tal requirements are decreased in those patients over 46 years of age. In that study, however, relatively few elderly patients were included. In a later retrospective study² of 540 patients, it was found that thiopental dosage requirements were decreased only in those patients over 60 years of age. This observation may be consistent with the fact that the elderly have a smaller lean body mass per total body weight than a young adult of equal weight and thus, the elderly require less drug for induction to "fill" this smaller mass. If one assumes that the site of action is associated with body regions highly perfused by blood and that this region therefore would form part of the volume of the central compartment, our data indicate no dependence of this volume upon age. Based upon that volume, therefore, induction doses of thiopental would also be independent of age. Arguing against this conclusion are the observations cited above which indicate the need to reduce induction doses in the elderly. Since our study was not designed to include assessment of response it is impossible for us to reach any conclusion, based upon our pharmacokinetic data, about the need to alter induction doses in the aged. The need to reduce the induction dose with age may be explained by altered sensitivity to the anesthetic. The adjustment of induction doses with age on a quantitative level remains to be solved.

The apparent volume of distribution may be altered

as a consequence of changes in body composition with age. It has been shown that total body water, both in absolute terms⁹ and as a percentage of body weight¹⁰ is decreased by 10 per cent to 15 per cent between the ages of 20 and 80 years. Lean body mass is also reduced in proportion to total body weight with advancing age. Novak,¹¹ in comparing young (18–25 years) with elderly (65–85 years) women, found that body fat increased from 33 per cent to 45 per cent, fat-free mass decreased from 67 per cent to 55 per cent and cell mass decreased from 38 per cent to 31 per cent. Drugs which are distributed into total body water or lean body mass might produce higher blood levels in the elderly when equal doses are given. This has been shown by Vestal *et al.*¹² for ethanol. For highly lipid-soluble drugs, increased body fat with advancing age may result in larger apparent volume of distribution because of drug accumulation into a larger physiologic space. In the present study, a strong correlation was found between age and the apparent volumes of distribution, V_d and V_{ss} . These results are consistent with the findings by Greenblatt *et al.*¹³ and Klotz *et al.*¹⁴ who reported that age was associated with a larger apparent volume of distribution for diazepam. This could explain the increase in half-life noted with advancing age. It should be stressed, however, that our data relate specifically to women.

Since unbound drug concentration is an important determinant of drug distribution and elimination, changes in the binding of drugs to serum proteins and changes

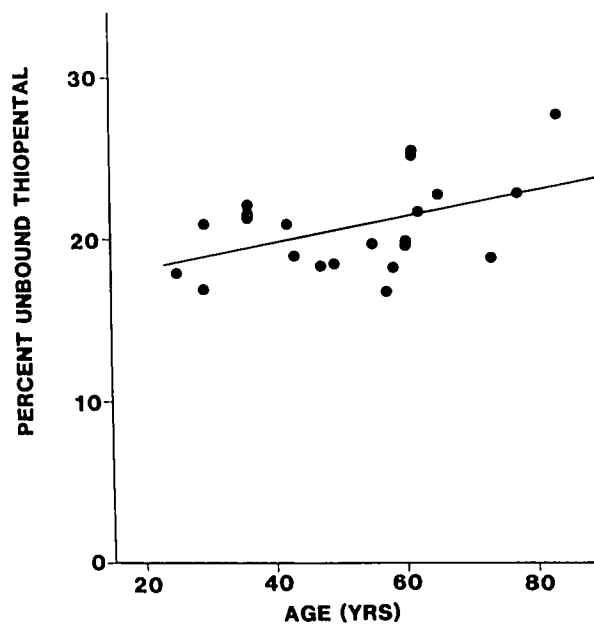


FIG. 5. Relationship between the per cent unbound thiopental (α) in serum and age. The solid line was determined by linear regression analysis ($r = 0.46$, $P < 0.05$).

in the blood to plasma ratio may potentially alter drug disposition in the elderly. In this study, a significant correlation between the free fraction of thiopental in serum and age was observed although age explains only about 21 per cent of the variation (*i.e.*, $r^2 = 0.21$). The free fraction, however, was not related to the concentration of serum albumin or serum protein. In contrast, Greenblatt *et al.*¹³ reported significantly larger free fractions of diazepam in the elderly (1.72 per cent) than in the young (1.23 per cent) as a result of decreased serum albumin concentration. In that study only 32 per cent of the total variation in free fraction could be explained by age and serum albumin concentration. Results from previous studies which have examined the effect of age on the serum protein binding of certain drugs are conflicting because of other confounding factors such as albumin concentration, disease states, and competition for binding sites with other co-administered drugs. Correction of the apparent volumes of distribution, V_β and V_{ss} , for differences in free fraction indicate that age is still the major determinant of the distribution of unbound thiopental. In contrast, the volume of distribution of unbound diazepam was not influenced significantly by age.¹³

Drug metabolism may be altered in the elderly, however, because of the lack of a quantitative index to assess the efficacy of hepatic drug metabolism, there are no direct studies on the effects of aging on the liver drug metabolizing enzymes in humans. In fact, Triggs and Nation¹⁵ concluded that there is no evidence for an age-related decline in the capacity of the liver to metabolize a drug. Indirect evidence suggests that in humans, advancing age may result in an alteration of the intrinsic metabolic capacity of the liver for some drugs that are metabolized extensively by the liver.

The metabolic clearance of antipyrine, which has been used widely as an index of microsomal drug oxidation, has been shown consistently to be reduced in elderly subjects.^{10,16,17} The reduced clearance of antipyrine may be due in part to an age-related decrease in functional liver volume and in part to decreased microsomal enzyme activity.¹⁸ An extensive study by Vestal *et al.*¹⁰ in 307 healthy male subjects showed that the large interindividual variation in the metabolic clearance of antipyrine exceeded the effect of age and only 3 per cent of the variance could be explained by age alone. It was concluded that genetic and environmental factors must be considered in examining drug metabolism in the elderly. Genetic factors, sex, age, and environmental factors make pharmacokinetic comparisons between the young and elderly groups difficult. In the present study, no significant difference was observed in either total body clearance or unbound clearance for thiopental with advancing

age. At present, no general relationships have been established between aging and drug metabolism.

It is of interest to compare our findings with those reported recently by Morgan *et al.*¹⁹ who examined thiopental disposition in five women. In general, the values of the pharmacokinetic parameter that we have obtained are in good agreement with those reported in that publication. For comparison purposes we have calculated the range of values for our patients aged 29–65 years (18 subjects) to correspond approximately to the age range of the patients studied by Morgan *et al.* (*i.e.*, 27–69 years). The following comparisons present our results followed by those of Morgan *et al.*: V_β (l/kg), 0.90–6.50 *vs.* 1.42–6.65; V_{ss} (l/kg), 0.83–4.59 *vs.* 0.93–3.07; clearance ($l \cdot kg^{-1} \cdot h^{-1}$), 0.125–0.291 *vs.* 0.078–0.278; $t_{1/2}$ (h), 5.0–20.6 *vs.* 9.7–12.7. Our values tend to encompass a larger range since we examined many more patients.

One discrepancy does exist, however, in that we found serum protein binding to be independent of thiopental concentration over the range of 0.05 to 10 $\mu g/ml$ (ca. 85 per cent bound). In contrast, the data of Morgan *et al.* indicate a concentration dependence (using equilibrium dialysis) with binding decreasing from 96.1 per cent at 0.05 $\mu g/ml$ to 84.2 per cent at 10 $\mu g/ml$. We can offer no definitive explanation for this difference in results.

The implications of our results for clinical practice must be drawn carefully. In the first few minutes following induction, little difference is seen in the decrease in thiopental plasma concentrations between the young and aged subjects; thus, emergence from an equivalent initial dose may follow the same time course. However, the increased half-life of thiopental may suggest caution in planning a "balanced technique" which involves repeated doses of thiopental, since emergence may be slower, dependent upon the cumulative dose. The equivalence in thiopental disposition at early times does not address the different cardiovascular response of aged patients; nor are differences in ED_{50} for induction dose considered here. Long-term disposition of thiopental is one of several factors which must be considered in the proper clinical use of the drug.

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