Chronic Alcohol Intake Does Not Change Thiopental Anesthetic Requirement, Pharmacokinetics, or Pharmacodynamics

Barry N. Swerdlow, M.D.,* Frederick O. Holley, M.D.,† Pierre O. Maitre, M.D.,* Donald R. Stanski, M.D.‡

The anesthetic requirements of chronic alcohols for induction of anesthesia with thiopental were investigated using an electroencephalographic (EEG) measure of thiopental's CNS drug effect and pharmacodynamic modeling to relate thiopental serum concentrations to drug effect. Eleven patients with a history of excessive alcohol intake were studied from an inpatient alcohol rehabilitation program and compared with nine control patients or volunteers who were social drinkers. The alcoholic population had consumed ethanol 9–17 days prior to the study. They had no evidence of acute intoxication or acute withdrawal at the time of the study. Five of the 11 alcoholic patients were restudied after 1 month of abstinence from alcohol consumption. Each study consisted of a thiopental infusion until EEG burst suppression (1–3 s of isoelectric signal) was achieved. Timed arterial and then venous blood samples were obtained for measurement of thiopental serum concentrations for up to 36 h. Pharmacokinetic differences between groups were analyzed using a three-compartment model. Power spectral analysis of the EEG allowed determination of spectral edge frequency. An inhibitory sigmoid E₃₅₀ pharmacodynamic model combined with an effect compartment was used to analyze concentration–response relationships and to provide an estimate of brain sensitivity to thiopental in the study populations. The thiopental anesthetic dose requirement using the EEG was not different between alcoholics and nonalcoholics. The mean dose requirement (±SD) of alcoholics was 823 ± 246 mg and the mean dose requirement of nonalcoholics was 733 ± 218 mg. There were no differences in thiopental pharmacokinetic and pharmacodynamic parameters between alcoholics and nonalcoholics. In the subgroup of five alcoholics who were studied approximately 1 month later, thiopental dose requirement, pharmacokinetics, and pharmacodynamics had not changed. These findings suggest that thiopental induction doses should not be routinely increased in chronic alcoholic patients. (Key words: Alcoholism. Anesthetics, intravenous: thiopental. Brain: electroencephalogram. Pharmacodynamics: thiopental. Pharmacokinetics: thiopental.)

ALCOHOLISM is the third leading cause of death and disability in the United States. Conservative estimates suggest that between 10 and 15 million Americans are afflicted with this disease. This large prevalence together with the association of alcoholism with trauma and with gastrointestinal hemorrhage make alcoholics frequent surgical patients.¹

It is commonly believed that chronic alcoholic patients require more intravenous (iv) barbiturate than normal for adequate induction of general anesthesia.²–⁴ To some extent this notion represents an extension from the belief in cross-tolerance to volatile anesthetics in alcohol-dependent individuals, in whom the MAC of halothane has been shown to be increased.⁵–⁶ The data on halothane MAC and alcohols has only been published in abstract form from 10 to 20 yr earlier. The clinical literature concerning barbiturate induction dose requirements in alcoholics, however, is confusing.⁷–⁹ Acute alcohol intoxication, associated drug abuse, acute alcohol withdrawal, and cardiovascular, renal, and hepatic dysfunction all may modify the iv induction dose–response relationship in alcoholic patients. These commonly associated conditions significantly complicate clinical studies involving this population and may account for some of the confusion in the literature.

For this reason in the current study we chose to examine a limited subset of the alcoholic population to isolate the specific effect of chronic alcohol consumption on thiopental induction dose requirement. Alcoholics were chosen from an inpatient alcohol rehabilitation program to assure that they had no alcohol consumption acutely or during the period between studies and had no evidence of the associated conditions detailed herein. To determine the effect of alcohol abstinence on any tolerance observed, a subgroup of the alcoholic population was restudied after 1 month of abstinence to determine if any change in anesthetic requirement had occurred over time.

Thiopental dose requirement was examined using an established model of thiopental anesthesia, which incorporates changes that are observed in the electroencephalogram (EEG) as a measure of the drug's effects on the brain.¹⁰ This model has been used successfully in the past to examine the phenomenon of acute tolerance to thiopental¹¹ as well as the effect of increasing age on thiopental requirement.¹² In addition to dose requirement, both the pharmacokinetics and pharmacodynamics of thiopental were studied to understand more clearly the nature of its dose–response relationship in alcoholics. Because the induction dose requirement of thiopental is de-
determined by its distribution pharmacokinetics and by brain sensitivity, differences in this dose requirement between alcoholics and nonalcoholics would be accounted for by one or both of these factors.

Methods

After institutional approval, informed consent was obtained from all patients. Two groups of patients were studied. The alcoholic group consisted of 11 ASA Physical Status 1 or 2 male patients in an inpatient alcohol rehabilitation program at the Palo Alto Veteran’s Administration Medical Center. Table 1 provides a detailed description of the alcoholic subjects’ age, weight, liver function, alcohol-related medical problems, and alcohol intake history. Two subjects had a previous history of drug abuse: subject 7 had used cocaine and subject 5 had occasionally used heroin approximately 1 month prior to admission. The rehabilitation program requires that all new patients abstain from drugs and alcohol for at least 3 days prior to admission. The average length of stay is approximately 90 days, but some patients stay as long as 6 months. No sedatives or hypnotics are allowed in this program. No patient at the time of the study had evidence of acute alcohol intoxication or withdrawal.

Five of these patients formed a subset of this group (repeat study group), which underwent repeat investigation after 1 month of supervised inpatient abstinence from alcohol. The control subjects were nine ASA Physical Status 1 or 2 patients (n = 3) or volunteers (n = 6) with no history of alcoholism. Six of the controls were volunteers and three subjects were surgical patients. The control subjects’ mean (±SD) age was 35 ± 6 yr and weight was 79 ± 15 kg. All members of the control group were social drinkers (i.e., consuming 1–3 glasses of wine per week) or abstained from alcohol. For both groups history, physical examinations, complete blood counts, urinalyses, and serum liver function tests were performed. The enrolled individuals had no evidence of cardiovascular, pulmonary, renal, or acute hepatic disease. One subject (4) in the alcoholic group had moderately abnormal liver function tests, and two subjects (1 and 11) had borderline liver function tests (table 1). Other measures of liver function (protein, albumin, prothrombin) paralleled the presented liver function tests.

Fasted, unmedicated subjects in both groups were brought to the postanesthetic recovery room. A standard electrocardiogram (ECG), blood pressure cuff, precordial stethoscope, and pulse oximeter were applied for monitoring. EEG electrodes were applied to the scalp according to the following configuration: FP1–O1, FP2–O2, Cz–O1, Cz–O2 (International 10–20 system of electrode placement; FP = frontoparietal region; O = occipital region; Cz = vertex of head; 1 = left side; 2 = right side). The raw EEG was continuously displayed on a Beckman Accutrace® EEG machine and recorded on FM magnetic tape via an eight-channel recorder (Vetter® model A) to allow subsequent off-line waveform analysis.

### Table 1. Subject Characteristics: Alcoholic Group

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Days since Last Drink</th>
<th>Liver Function*</th>
<th>Alkaline Phosphatase</th>
<th>Alcohol-related Medical Problems</th>
<th>Alcohol Intake History</th>
</tr>
</thead>
<tbody>
<tr>
<td>1†</td>
<td>45</td>
<td>67</td>
<td>10</td>
<td>60/114</td>
<td>128</td>
<td>Withdrawal seizures</td>
<td>Vodka: 1 quart/day, 2 yr</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>83</td>
<td>10</td>
<td>12/32</td>
<td>85</td>
<td>Blackouts§</td>
<td>prior pint/day × 10 yr</td>
</tr>
<tr>
<td>3†</td>
<td>43</td>
<td>76</td>
<td>9</td>
<td>40/17</td>
<td>79</td>
<td>Withdrawal seizures</td>
<td>Hard liquor 1 quart/day</td>
</tr>
<tr>
<td>4†</td>
<td>37</td>
<td>77</td>
<td>10</td>
<td>221/342</td>
<td>124</td>
<td>None</td>
<td>Gin: 1 quart/day × 15 yr</td>
</tr>
<tr>
<td>5</td>
<td>31</td>
<td>82</td>
<td>13</td>
<td>12/32</td>
<td>82</td>
<td>History of hepatitis B</td>
<td>Hard liquor 1 quart/day</td>
</tr>
<tr>
<td>6†</td>
<td>30</td>
<td>75</td>
<td>14</td>
<td>24/32</td>
<td>86</td>
<td>Withdrawal seizures</td>
<td>during binges × 23 yr</td>
</tr>
<tr>
<td>7†</td>
<td>36</td>
<td>64</td>
<td>17</td>
<td>13/17</td>
<td>97</td>
<td>Blackouts§</td>
<td>Vodka: 1 quart/day × 15 yr</td>
</tr>
<tr>
<td>8</td>
<td>42</td>
<td>86</td>
<td>9</td>
<td>19/36</td>
<td>113</td>
<td>Delirium tremens</td>
<td>Beer: 12 cans/day × 15 yr</td>
</tr>
<tr>
<td>9</td>
<td>29</td>
<td>71</td>
<td>13</td>
<td>24/55</td>
<td>63</td>
<td>Blackouts§</td>
<td>Vodka: 1 quart/day × 3 yr</td>
</tr>
<tr>
<td>10</td>
<td>31</td>
<td>84</td>
<td>15</td>
<td>NA/45</td>
<td>117</td>
<td>Blackouts§</td>
<td>Beer: 12 cans/day × 3 yr</td>
</tr>
<tr>
<td>11</td>
<td>39</td>
<td>118</td>
<td>10</td>
<td>50/50</td>
<td>175</td>
<td>Delirium tremens</td>
<td>Beer: 12–18 cans/day × 14 yr</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>37 ± 6</td>
<td>80 ± 14</td>
<td>12 ± 3</td>
<td></td>
<td></td>
<td></td>
<td>Whiskey: 1–2 pints/day</td>
</tr>
</tbody>
</table>

NA = not available. One quart is approximately 1 l; 1 pint is approximately 0.5 l; 1 can of beer is approximately 300 ml.
* Normal values: SGOT, 0–41; SGPT, 0–45 U/l.
† Normal value: alkaline phosphatase: 30–115 U/l.
‡ Subject studied twice.
§ An alcoholic blackout can be described as a temporary amnesia for the alcoholic, but for the people around the alcoholic at the time the behavior is normal, i.e., working, sleeping, playing, regular conversation.
† Duration of alcohol abuse could not be accurately determined from the subject.
An antecebal iv and a radial arterial catheter were inserted in opposite arms in each subject using local anesthesia. Blood pressure and heart rate were continuously recorded throughout the study and arterial blood gases sampled intermittently to assure normocarbia. All patients were allowed to breathe mask oxygen via a nonrebreathing system during 5 min of baseline EEG recording. Thereafter, sodium thiopental was infused intravenously at a rate of 100 mg/min until the EEG demonstrated bursts of electrical activity separated by 3-s isoelectric intervals–burst suppression (Stage 3). This end point defined thiopental dose requirement. At this time the thiopental infusion was terminated and the patients were allowed to regain consciousness. Ventilation was assisted as necessary throughout the anesthetic period if clinical evidence of hypoventilation was seen.

Frequent arterial blood samples were obtained during the thiopental infusion and for 50 min thereafter. At that time EEG recording was terminated and venous blood samples were drawn at 2- to 6-h intervals for up to 36 h. Thiopental serum concentrations were determined in all samples by high-performance liquid chromatographic assay sensitive to 100 ng/ml with a coefficient of variation of 2.9% at 5 μg/ml.

### DATA ANALYSIS

Serum concentration versus time data for each patient were fit to two- and three-compartment pharmacokinetic models adjusting for the drug infusion using extended least-squares nonlinear regression. In all patients a three-compartment model provided a statistically better fit using the log likelihood value. Optimal data weighting was determined by the extended least squares criteria of the regression program. Values for the following pharmacokinetic parameters were derived from the three-compartment model fit: the volume of the central compartment ($V_c$), the volume of distribution at steady state ($V_{ss}$), intercompartmental clearance, metabolic clearance, and terminal half-life using standard formulas.

The EEG pharmacodynamic data were analyzed as follows. A digital PDP 11/23 computer was utilized to perform off-line power spectral analysis of the EEG recorded on FM magnetic tape in a manner previously described. The signal was digitized at a rate of 200 Hz with 10 bit resolution and divided into 5.12-s epochs. Fast Fourier analysis then transformed these data into voltage and frequency (resolved to 0.4 Hz) components. Voltage was squared to give power and power plotted as a histogram versus frequency to produce a compressed spectral array. The spectral edge of each epoch was determined as the frequency below which 95% of the power lies. As such, the spectral edge was used to characterize the degree of EEG activation or slowing and to model the depth of thiopental anesthesia. Noise in this spectral edge data was minimized by use of a curve smoothing technique with a moving arithmetic mean of ten consecutive epochs.

Nonlinear regression was then used to relate the spectral edge between EEG Stages 1 and 3 to thiopental concentrations employing the following inhibitory sigmoid pharmacodynamic model:

$$SE(t) = E_0 - \left(\frac{E_{\text{max}} \times C(t)^\gamma}{[IC_{50}^\gamma + C(t)^\gamma]}\right)$$

where $SE(t)$ is the spectral edge (Hz) at time $t$, $E_0$ is the baseline spectral edge (Hz) during EEG Stage 1, $E_{\text{max}}$ is the maximal decrease in spectral edge (Hz) due to thiopental, $IC_{50}$ is the predicted thiopental concentration (μg/ml) associated with 50% maximal decrease in spectral edge and hence a steady state estimate of brain sensitivity to thiopental, $\gamma$ is an exponent describing the steepness of the effect–concentration relationship, and $C(t)$ is the estimated thiopental concentration in the effect compartment at time $t$.

This model utilized an effect compartment in which drug effect is directly proportional to drug concentration in the effect compartment to adjust for the temporal lag between thiopental serum concentration and spectral edge change. A first-order rate constant ($K_{on}$) characterized the equilibration between the serum and effect site.

### STATISTICAL ANALYSIS

Dose to burst suppression and values for pharmacokinetic and pharmacodynamic parameters were compared between groups. For comparison of data between the alcoholic group and the control group, arithmetic means and standard deviations were calculated as well as 95% confidence intervals. When the 95% confidence interval for the difference of the means included 0, no difference could be shown between the two group values ($P > 0.05$). The statistical analysis was performed on the estimated elimination and equilibration rate constants, not the derived half-lives. Mean values for the elimination and equilibration half-lives were calculated from the corresponding mean values of the rate constants. Statistical comparison of first and second study data for alcoholic patients who underwent repeat study (repeat study group) was made using a paired two-tailed $t$ test. A $P$ value of $<0.05$ was considered significant.

### Results

The subjects in the control group, alcoholic group, and repeat study group did not differ significantly in age or weight. All of the alcoholic group patients had a history.

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of significant chronic alcohol intake. The dose range of ethanol was 2.4 to 6.3 ml·kg⁻¹·day⁻¹. By comparison, a 70-kg social drinker who consumes one-fourth of a bottle of wine (10% ethanol) per day would ingest 0.3 ml·kg⁻¹·day⁻¹. The mean time from last drink to the study for the alcoholic group was 12 ± 3 (SD) days, and for the repeat study group 43.2 ± 2.2 days from the last drink to the second study. Although the evaluation of alcohol intake will always remain subjective, the data indicated in table 1 were obtained by both experienced alcohol rehabilitation personnel and the investigators.

All alcoholic subjects entered the rehabilitation program on a voluntary basis because of the excessive alcohol consumption causing impairment of employment and social and personal relationships. The nutritional status of the alcoholic subjects was good, possibly explaining why the liver function tests in table 1 were not markedly abnormal given the reported alcohol intake.

There were no significant differences in the thiopental dose required to achieve EEG burst suppression in the alcoholic group versus the control group, or between alcoholics before (alcoholic group) and after 1 month of abstinence from alcohol consumption (repeat study group) (table 2; fig. 1).

Consistent with no difference in thiopental dose requirement, there were no statistically significant differences between the values of any of the pharmacodynamic parameters determined for the alcoholic group and the control group (table 2). Specifically, the rate of equilibration between thiopental serum concentration and pharmacologic effect (Kₜₘₙₐₓ), the brain's maximal EEG response to thiopental (Eₜₘₐₓ), and the steady state plasma concentration needed to cause one-half of the maximal EEG slowing (IC₅₀) were not demonstrably different. These same pharmacodynamic parameters did not change after 1 month's abstinence in the five alcoholic patients restudied after that interval. IC₅₀ was essentially unchanged after 1 month in four of these five patients (fig. 2). Hence, no difference in brain sensitivity to thiopental could be shown between alcoholics and nonalcoholics, nor was there any change in brain sensitivity associated with abstinence from alcohol consumption in the alcoholic population.

A retrospective power analysis was performed on the thiopental dose requirement difference between the alcoholic versus control subjects. To detect a difference in dose requirement of 33% using an unpaired t test with a P value of 0.05, the power of our sample size (n = 10) was 0.6. To detect a 50% difference in thiopental dose requirement, our sample size would have a power of >0.90.

Likewise, values for pharmacokinetic parameters did not show a significant difference between groups (table 3; fig. 3). Interestingly, there was no significant difference in elimination clearance or elimination half-life between alcoholics and nonalcoholics. Furthermore, there was no appreciable change in the pharmacokinetics of thiopental in alcoholics after abstinence for 1 month (repeat study group).

**Discussion**

Clinical impressions have suggested that chronic alcoholic patients are relatively resistant to the cerebral depressant effects of barbiturates and consequently require

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**Table 2. Pharmacodynamic Characteristics**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Dose Requirement (mg)</th>
<th>Eₜₘₐₓ (Hz)</th>
<th>IC₅₀ (µg/ml)</th>
<th>γ</th>
<th>Kₜₘₐₓ (min⁻¹)</th>
<th>Tₜₘₐₓ/γKₜₘₐₓ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>9</td>
<td>733 ± 218</td>
<td>17.2 ± 4.4</td>
<td>18.6 ± 5.7</td>
<td>3.2 ± 1.3</td>
<td>0.46 ± 0.15</td>
<td>1.5</td>
</tr>
<tr>
<td>Alcoholic</td>
<td>11</td>
<td>823 ± 246</td>
<td>16.1 ± 4.7</td>
<td>19.7 ± 4.2</td>
<td>3.2 ± 1.3</td>
<td>0.40 ± 0.13</td>
<td>1.7</td>
</tr>
<tr>
<td>Repeat study group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First study</td>
<td>5</td>
<td>680 ± 199</td>
<td>14.2 ± 3.9</td>
<td>19.3 ± 4.9</td>
<td>4.2 ± 1.1</td>
<td>0.36 ± 0.06</td>
<td>1.9</td>
</tr>
<tr>
<td>Repeat study</td>
<td>5</td>
<td>577 ± 133</td>
<td>15.9 ± 3.7</td>
<td>18.0 ± 5.5</td>
<td>3.6 ± 1.3</td>
<td>0.56 ± 0.16</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

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**Fig. 1.** The thiopental dose needed to achieve burst suppression with 5 s of isoelectric EEG during a constant infusion of 100 mg/min. The mean value is indicated with a +. The individual alcoholic subjects who were studied a second time are indicated with a connecting line.
larger than normal doses of thiopental for satisfactory induction of general anesthesia. This is purported to be true in patients who are not acutely intoxicated but rather have a history of increased alcohol consumption. Such cross-tolerance to barbiturates in alcohol-tolerant individuals, however, has never been adequately characterized.

Lee et al. found a trend that was not statistically significant toward increased anesthetic induction times in ethanol-tolerant rodents after intraperitoneal injection of thiopental. Employing a similar model, however, Newman et al. demonstrated an ethanol-related resistance to diazepam but not to thiopental by measuring loss of righting reflex, escape from a hot plate, and sleeping time. The same authors have subsequently documented a lack of cross-tolerance in this model between ethanol and the other short-acting barbiturates, methohexitol, thiopental, and secobarbital, although, interestingly, they did find cross-tolerance with pentobarbital and phenobarbital.

Human data concerning this issue are conflicting. In a study of women with a history of mild-to-moderate ethanol consumption undergoing therapeutic abortions, alcohol intake could not be correlated with differences in thioental induction time or quality. Of note, however, alcoholic patients did awaken earlier and at higher venous barbiturate serum concentrations. Venous thiopental serum concentrations are difficult to interpret when collected during the rapid redistribution phase because of the unknown effect of local extremity tissue uptake.

Milligan et al. have recently demonstrated an increased thiopental induction requirement in a relatively large population of individuals with a history of increased alcohol consumption. However, they did not exclude coexisting polydrug abuse or early ethanol withdrawal and employed a subjective end point that is a measure of a relatively light level of CNS depression, i.e., loss of either eyelid reflex or verbal contact.

An important reason for these varying results is the previous lack of a quantitative method for assessing thiopental anesthetic effect. Clinical observations in patients and behavioral assays in animals represent quantal rather than continuous responses and therefore can be imprecise. Furthermore, in the analysis of data concerning differences in thiopental requirements, many studies have not distinguished between changes in drug disposition (pharmacokinetics) and true changes in cerebral sensitivity.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>( V_1 ) (l)</th>
<th>( V_4 ) (l)</th>
<th>Metabolic Clearance (l/min)</th>
<th>Rapid and Slow Intercompartmental Clearance (l/min)</th>
<th>Elimination Rate Constant (min^-1)</th>
<th>Elimination Half-life (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>9</td>
<td>5.0 ± 2.2</td>
<td>128 ± 43</td>
<td>0.240 ± 0.086</td>
<td>2.2 ± 0.8</td>
<td>0.00151 ± 0.00071</td>
<td>457</td>
</tr>
<tr>
<td>Alcoholic</td>
<td>11</td>
<td>6.0 ± 1.8</td>
<td>152 ± 61</td>
<td>0.300 ± 0.080</td>
<td>2.6 ± 0.6</td>
<td>0.00149 ± 0.00036</td>
<td>463</td>
</tr>
<tr>
<td>Repeat study group</td>
<td>5</td>
<td>5.6 ± 1.8</td>
<td>129 ± 53</td>
<td>0.259 ± 0.082</td>
<td>3.0 ± 0.3</td>
<td>0.00157 ± 0.00041</td>
<td>440</td>
</tr>
<tr>
<td>First study</td>
<td>5</td>
<td>5.6 ± 2.2</td>
<td>131 ± 39</td>
<td>0.262 ± 0.086</td>
<td>3.0 ± 1.1</td>
<td>0.00192 ± 0.00031</td>
<td>525</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
(pharmacodynamics). Also, the use of venous arm blood sampling to characterize distribution pharmacokinetics may obscure differences in thiopental pharmacokinetics.

Computerized power spectral analysis of the EEG has been shown to provide a continuous and quantitative measurement of the progression between clinically recognized EEG stages of thiopental anesthesia. Thus, the progress toward and achievement of an EEG end point can quantitate a dose–response relationship for thiopental in a precise fashion. In addition, statistical and pharmacokinetic/dynamic modeling theory has developed to permit generalization about steady state pharmacodynamics from input of drug concentrations and effects measured under nonequilibrium conditions. In conjunction with standard pharmacokinetic modeling, this approach allows for understanding of the dose–response relationship in terms of dose–concentration (pharmacokinetic) and concentration–response (pharmacodynamic) information. Specifically, it permits estimation of the brain sensitivity to thiopental, as measured by \( E_{\text{max}} \) and \( IC_{50} \) in the inhibitory sigmoid \( E_{\text{max}} \) pharmacodynamic model employed here.

Surprisingly, when this approach was utilized to examine the question of tolerance of alcoholics to thiopental as an anesthetic induction agent, no such tolerance could be demonstrated. There were no statistically significant pharmacokinetic or pharmacodynamic differences between alcoholics and nonalcoholics. Not only were initial volumes of distribution and distribution clearance of thiopental similar in alcoholics and nonalcoholics, but there was no difference in \( IC_{50} \) (and thus brain sensitivity) between the two populations. Furthermore, \( IC_{50} \) was remarkably constant in those patients studied twice, a powerful validation of this modeling technique (table 2).

The assumption that alcoholics require more barbiturate for adequate anesthetic induction has to some extent been an extension from notions concerning MAC and volatile anesthetics. Even for MAC, however, experimental studies in humans are limited to abstracts showing increased halothane MAC in a small number of human alcoholics. Additional support to this notion is provided only by a small number of studies involving halothane or isoflurane cross-tolerance in alcohol-fed rodents.

Because our pharmacodynamic assessment was performed 9–17 days after the last consumption of ethanol, it is possible that the tolerance to both the ethanol and other concurrent CNS depressants had dissipated. In a mouse model of chronic ethanol administration, Goldstein and Zaechelein demonstrated that the tolerance to ethanol decayed progressively and was no longer appreciable 30 h after withdrawal. Comparable quantitative data for humans and the dissipation tolerance to other CNS depressant drugs are not available.

No clinical condition has been clearly demonstrated in humans to change thiopental CNS sensitivity. Early studies first suggested the concept of acute tolerance to thiopental in reporting that subjects receiving larger doses of thiopental had higher plasma concentrations at the time of awakening than did those receiving smaller ones. Using methodology similar to that employed in the present study, however, Hudson et al. were unable to demonstrate evidence of acute tolerance to thiopental EEG effects. Likewise, Homer and Stanski showed that the age-related decrease in thiopental dose requirement is a function of altered distribution kinetics and not secondary to a change in brain sensitivity.

Thiopental induction requirement reflects not only brain sensitivity but also initial distribution pharmacokinetics. As such, the finding of unchanged induction doses in the alcoholic population considered here is also a function of the fact that this group did not manifest significantly abnormal initial volumes of distribution or rates of distribution. Couderc et al., in a study involving venous blood sampling, have similarly shown normal values for initial distribution volume in noncirrhotic alcoholic patients. Unlike the present study, however, Couderc et al. found an increased plasma clearance of thiopental in alcoholics (although no decrease in terminal elimination half-life). However, all patients in this latter study had abnormal liver function tests. This contrasts with the alcoholic group considered in the present study, and as such, these differences may reflect different states of liver enzyme induction.

The finding of normal thiopental pharmacokinetics and pharmacodynamics in alcoholics using an EEG model of general anesthesia is a surprise when considered in the context of common clinical impressions. Its applicability to the clinical setting is strongly suggested by the association of EEG end points with clinical end points, not only for barbiturates but also for other iv anesthetics. As such, a priori increases in barbiturate induction doses in uncomplicated alcoholic patients are probably unwarranted and potentially dangerous. Selection of thiopental induction dose values, rather, should be based on factors known to alter initial drug distribution kinetics as well as on standard hemodynamic considerations. Although brain sensitivity to thiopental is not altered in the alcoholic population considered in the present study, alcoholics acutely intoxicated or acutely withdrawing may well represent separate subgroups with altered CNS responses to iv anesthesia.

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References
ALCOHOLISM AND THIOPENTAL DOSE REQUIREMENT