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Abstract

Barbiturate coma is initiated in brain-injured patients whenever elevated intracranial pressure remains unresponsive to other therapeutical strategies. However, barbiturates alter cortical activity resulting in difficulties in clinical evaluation. Therefore, we investigated the impact of long-term thiopental administration on responsiveness to exteroceptive stimuli in relation to pharmacokinetics of thiopental in CSF and serum. Long-term infusion increases thiopental levels which remain elevated for 6 and 9 days in CSF and serum, respectively, after termination of its administration. Prolonged unresponsiveness to exteroceptive stimuli correlates with persisting thiopental in CSF and serum. Thus, quantitative analysis of thiopental in serum becomes indispensable in predicting the length of drug-induced neurological impairment and in avoiding misinterpretation of the neurological status.
Thiopental in CSF and Serum Correlates with Prolonged Loss of Cortical Activity

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Key Words
Thiopental
Traumatic brain injury
Drug kinetics
Drug monitoring
Barbiturate coma
Electroencephalogram

Abstract
Barbiturate coma is initiated in brain-injured patients whenever elevated intracranial pressure remains unresponsive to other therapeutical strategies. However, barbiturates alter cortical activity resulting in difficulties in clinical evaluation. Therefore, we investigated the impact of long-term thiopental administration on responsiveness to exteroceptive stimuli in relation to pharmacokinetics of thiopental in CSF and serum. Long-term infusion increases thiopental levels which remain elevated for 6 and 9 days in CSF and serum, respectively, after termination of its administration. Prolonged unresponsiveness to exteroceptive stimuli correlates with persisting thiopental in CSF and serum. Thus, quantitative analysis of thiopental in serum becomes indispensable in predicting the length of drug-induced neurological impairment and in avoiding misinterpretation of the neurological status.

Introduction
Patients suffering from severe traumatic brain injury require close monitoring to prevent irreversible neurological damage. Secondary brain injuries due to reduced cerebral perfusion [1], disturbed ionic homeostasis [2], released excitotoxic transmitters [3, 4], generated free radicals [5], and depleted energy stores [6] can lead to post-traumatic increases in intracranial pressure (ICP). To avoid secondary brain damage due to elevated ICP, different strategies are applied, e.g., head elevation, controlled hyperventilation, administration of mannitol, and drainage of CSF [7]. These measures, however, may fail to reduce elevated ICP and a more aggressive therapeutic strategy as the administration of barbiturates may become indispensable. The beneficial effect of barbiturates in terms of lowering elevated ICP is thought to be due to a decrease in cerebral metabolism and blood flow [8, 9].

Thiopental is the most commonly applied barbiturate in patients with severe traumatic brain injury and life-threatening ICP elevations. Serum thiopental levels found to induce the burst-suppression pattern in EEG are greater than 40 μg/ml, while blood values exceeding 70 μg/ml may suppress cerebral activity completely [10]. Considering the lipophilicity of barbiturates, concentrations in CSF should follow the changes in blood [11] and thiopental should persist for some time after termination of long-term infusion.

Clinical experience shows that these patients remain in a prolonged come-like state even after thiopental infusion.
Table 1. Epidemiological data in severely brain-injured patients receiving thiopental

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age years</th>
<th>History and clinical findings</th>
<th>Surgical procedures</th>
<th>Duration of intensive care, days</th>
<th>GOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>♂</td>
<td>27</td>
<td>15 ft. free fall with skull fracture and global cerebral edema</td>
<td>VO NEML</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>♂</td>
<td>48</td>
<td>7 ft. free fall with skull fractures, frontoparietal contusions, SDH and SAH</td>
<td>VO EML</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>♂</td>
<td>24</td>
<td>15 ft. free fall with frontotemporal contusions and SDH</td>
<td>VO EML</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>♂</td>
<td>24</td>
<td>MVA with bifrontal and occipital contusions</td>
<td>VO NEML</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>♂</td>
<td>16</td>
<td>skull fractures and frontal contusions from falling object</td>
<td>VO NEML</td>
<td>34</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>♂</td>
<td>31</td>
<td>12 ft. free fall with SDH and EDH and frontal contusions</td>
<td>VO EML</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>♂</td>
<td>19</td>
<td>MVA with skull fractures and bifrontal contusions</td>
<td>VO NEML</td>
<td>28</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>♂</td>
<td>25</td>
<td>unknown cause skull base fracture with bifrontal and temporal contusions and EDH</td>
<td>VO EML</td>
<td>28</td>
<td>5</td>
</tr>
<tr>
<td>Average</td>
<td>6 ♂, 2 ♂</td>
<td>27±10</td>
<td></td>
<td></td>
<td>28±4</td>
<td></td>
</tr>
</tbody>
</table>

Results are given as mean ± SD. MVA = Motor vehicle accident; EDH, SDH, SAH = epi-, subdural, subarachnoid hemorrhage; VO = ventriculostomy; EML/NEML = evacuated mass lesion/nonevacuated mass lesion.

has been discontinued days before. Our assumption is that thiopental persists in CSF and serum in relevant amounts to influence cerebral activity after stopping long-term barbiturate infusion. Until now, however, there are no data available which correlate thiopental levels in CSF and serum with prolonged altered cerebral activity after long-term thiopental infusion. As discussed by others, clinical evaluation is very difficult when patients are subject to long-term barbiturate infusion [12] and it cannot be excluded that high-dose barbiturate treatment itself might negatively influence posttraumatic functional recovery [13]. Therefore, the aim of this study was to investigate the impact of CSF and serum thiopental levels on cortical activity as assessed by EEG during and after long-term barbiturate infusion in severely brain-injured patients.

Patients and Methods

Patients included in this study suffered from severe traumatic brain injury (Glasgow Coma Score <9). After admission patients were taken to surgery for evacuation of any hematomas and implantation of intraventricular or subdural catheters. Thereafter, the intubated and mechanically ventilated patients were treated according to a standard protocol [7]. The critical care management goal was to maintain cerebral perfusion pressure above 70 mm Hg, which was accomplished by maintaining ICP below 20 mm Hg and mean arterial pressure above 90 mm Hg. All patients were analgesedated with fentanyl and midazolam and relaxation was achieved with pancuronium. The decision to commence barbiturate coma was based solely on clinical grounds. Patients suffering from persisting ICP values exceeding 20 mm Hg received thiopental intravenously, provided that ICP could not be lowered by routine measures such as drainage of CSF or controlled hyperventilation. Barbiturate coma was induced by giving thiopental (Pentothal® Abbott Laboratories, Switzerland) 5–11 mg/kg body weight as a bolus, followed by continuous infusion of 4–6 mg/kg/h to maintain a burst-suppression pattern of
Fig. 1. Changes in serum (●; a) and CSF (●; b) thiopental concentrations during and after long-term thiopental infusion. The numbers of patients receiving thiopental are shown for each day. Results are given as µg/ml ± SD. The bold line depicts the estimated decline of thiopental based on an average elimination half-life of 24 h [25].

Thiopental in CSF and Serum Prolongs Coma

4–6 bursts/min. Cortical activity and responsiveness to exteroceptive painful and acoustic stimuli was assessed by routine 12-channel EEG analysis before commencing barbiturate coma. During the actual period of barbiturate coma EEG was recorded continuously and the burst-suppression pattern was used to adjust the dosage of thiopental. Barbiturate coma was stopped once ICP remained below 20 mm Hg for 48 h. Responsiveness was assessed daily until normal activity reappeared. Neurological outcome was evaluated 6 months after the initial trauma using the Glasgow Outcome Score (GOS) [14]. This numeric scale attempts to describe the different possible degrees of neurological outcome: 1 = deceased patients; 2 = persistent vegetative state; 3 = severe disability (conscious but disabled); 4 = moderate disability (disabled but independent); 5 = good recovery.

After approval by the local ethics committee, CSF and paired arterial blood samples of 8 patients, chosen at random, were drawn every morning. After immediate centrifugation, samples were stored at −70°C until further analysis by HPLC and UV detection at 280 nm [15]. All samples were measured as duplicates and results are shown as µg/ml ± SD. Changes in CSF and serum thiopental concentrations were examined by analysis of variances (ANOVA) and mutual dependency of the different parameters was computed by linear regression. Differences were rated statistically significant whenever p < 0.05.

Results

Patients

From 1994 to 1996 a total of 386 severely brain-injured patients were treated at our Intensive Care Unit (ICU) of whom 32 patients were subject to long-term thiopental infusion due to otherwise untreatable increases in ICP. Of these 32 patients, 24 (75%) survived whereas 8 patients (25%) succumbed to malignant intracranial hypertension. Incidentally, the 8 patients chosen for the present prospective investigations belong to the group of survivors. Two female and 6 male patients with an average age of 27 ± 10 years suffered from severe traumatic brain injury and life-threatening ICP elevations. Surgical removal of subdural and/or epidural hematomas became necessary in 4 patients before administration of barbiturates. All patients were treated in the ICU for 28 ± 4 days (table 1). With the exception of 1 patient (No. 1), who remained severely disabled, all others showed a moderate to good outcome (GOS 4–5), as estimated by the GOS 3–6 months after the trauma.

Thiopental

Patients in this study received thiopental intravenously for an average duration of 7 ± 3 days (2–10 days). Total daily amounts administered ranged from 750 to 9,625 mg/24 h (2,512 ± 1,720 mg/24 h). During infusion of thiopental the concentrations increased significantly in serum and CSF. Serum thiopental levels rose continuously from 15.0 ± 16.7 (day 1) to 52.1 ± 31 (day 2), and 101.2 ± 21.0 µg/ml (day 8) (fig. 1a). The therapeutic threshold of 40 µg/ml was reached or surpassed in 7 of 8 patients and the maximal values ranged from 20.7 to 130.8 µg/ml (table 2). CSF concentrations changed in a similar manner (fig. 1b) as seen in serum and increased steadily from 2.0 ± 1.7 (day 1) to 4.6 ± 2.8 (day 2) and 8.7 ± 4.9 µg/ml (day 9). The maximal CSF values ranged from 4.1 to 13.4 µg/ml (table 2). These elevations, however, did not correlate with the total amount of thiopental administered each day. Thiopental concentrations in CSF ranged from 6 to 33% of the corresponding serum values and were increased dose-dependently by the serum levels (CSF thiopental = 1.29 × serum thiopental; n = 35; r = 0.81; p < 0.001). After terminating thiopental infusion, the levels in serum and CSF decreased during the
Fig. 2. Persisting loss of responsiveness to exteroceptive stimuli in dependence of prolonged clearance of thiopental from CSF (●) and serum (○). (CSF: days of absent cortical activity = 0.26 + 1.74 × maximal days of thiopental persistence in CSF; n = 8; r = 0.87; p = 0.005; serum: days of absent cortical activity = −1.17 + 1.29 × maximal days of thiopental in serum; n = 8; r = 0.81; p = 0.007.)

Table 2. Detection of peak concentrations of thiopental in CSF and serum (μg/ml) during long-term infusion

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Detection of thiopental after termination of Pentothal® infusion, days in CSF</th>
<th>Persistence of absent responsiveness, days</th>
<th>Maximal thiopental levels in CSF, μg/ml</th>
<th>Maximal thiopental levels in serum, μg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>4.7</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>10.5</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>5</td>
<td>6</td>
<td>7.7</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>9</td>
<td>12</td>
<td>13.4</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>7</td>
<td>6</td>
<td>9.9</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>8.9</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>4.05</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>6</td>
<td>7</td>
<td>4.1</td>
</tr>
<tr>
<td>Average ± SD</td>
<td>3.4 ± 1.3</td>
<td>5.6 ± 1.8</td>
<td>6.1 ± 2.6</td>
<td>7.9 ± 3.4</td>
</tr>
</tbody>
</table>

Thiopental levels in CSF and serum persist with a prolonged absence of responsiveness (days) after stopping long-term thiopental infusion. All results are shown as mean ± SD.

following 6–9 days by a zero-order process. When calculating the disappearance of thiopental based on the maximally attained concentrations and an average elimination half-life of 24 h, the measured decline corresponds very well to the estimated disappearance rate (fig. 1a, b). The clearance itself correlated neither with the duration nor the total amount of thiopental given during the infusion period but correlated with the maximal levels as measured in CSF (days of persistence = 0.76 + 0.33 × maximal thiopental in CSF; n = 8; r = 0.87; p = 0.008) and serum (days of persistence = 2.66 + 0.04 × maximal thiopental in serum; n = 8; r = 0.85; p = 0.007). Thiopental in CSF disappeared with an average of 2.3 ± 1 days before thiopental was no longer detectable in serum (fig. 1a, b; table 2).

**EEG Changes**

Administered thiopental induced the characteristic burst-suppression pattern in EEG in all patients. Absent cortical responsiveness to exteroceptive stimuli persisted 4–12 days after stopping barbiturate infusion, with an average of 6.1 ± 2.6 days (table 2). Duration of absent responsiveness correlated with maximal thiopental levels found in CSF (days of absent responsiveness = 1.33 + 0.61 × maximal CSF thiopental; n = 8; r = 0.8; p = 0.017). The length of absent responsiveness correlated with the persistence of thiopental in CSF and serum (fig. 2) (CSF: n = 8; r = 0.87; p = 0.005; serum: n = 8; r = 0.81; p = 0.007).
Discussion

Administration of barbiturates in brain-injured patients may successfully decrease otherwise untreatable and life-threatening ICP elevations and may ameliorate neurological outcome [16, 17]. Thiopental, the ‘ultrashort acting’ barbiturate [18], is commonly applied in the intensive care of brain-injured patients. Thiopental inhibits electrical activity of the brain by increasing the conductance of GABA\(_\alpha\)-regulating chloride channels [19]. This, in turn, reduces overall oxygen consumption by approximately 50%, which corresponds to the energy requirement of neuronal function [8]. This downregulation of cortical electrical activity results in altered wave and frequency distribution in the EEG. The most specific finding of barbiturate coma is the burst-suppression pattern, which consists of isolated neuronal excitation in an otherwise silent brain, characterized by an isoelectric line in the EEG.

Patient Population

The 8 subjects investigated in the present study belong to a small subgroup of patients requiring barbiturate coma (n = 32) who are taken from a large series of severely brain-injured patients (n = 386) treated at the University Hospital in Zürich. Overall, they are only representative of the other 16 patients surviving barbiturate coma but not of all head-injured patients.

Changes in Serum and CSF Thiopental

During long-term infusion, thiopental in serum and CSF increases significantly, ranging from 3.5 to 130.8 \(\mu g/ml\) in serum and from 0.7 to 13.4 \(\mu g/ml\) in CSF (table 2). As shown in this study and reported by others [20, 21], blood and CSF barbiturate levels, however, do not correlate with the dosage given and cannot predict the depth of anesthesia. This is best explained by characteristic redistribution phenomena of barbiturates in different compartments [22, 23]. Nevertheless, the threshold of 40 \(\mu g/ml\) in serum, which has been shown to induce burst-suppression is surpassed in all patients but 1 [10]. Our data show that serum thiopental levels increase the CSF concentrations dose-dependently. Once lipophilic tissues are saturated, CSF concentrations are equivalent to thiopental levels of the brain and changes in serum are immediately reflected by changes in CSF [11]. The CSF levels as measured here correspond to 6–33% of the paired serum values which allow to calculate a threshold between 2.4 and 13.2 \(\mu g/ml\) for thiopental in CSF which is necessary to induce burst-suppression. These are similar concentrations as found capable of controlling cortical hyperactivity in status epilepticus [24]. Elevation in CSF thiopental seen in these patients with severe traumatic brain injury is most likely due to the lipophilicity of thiopental.

After short-term application of thiopental, the average elimination half-life of thiopental is 12 h [25]. The pharmacokinetic behavior of low-dosage thiopental follows a first-order kinetic and a constant fraction of this barbiturate is eliminated hepatically, while the rate of elimination and half-life is independent of the blood concentration. However, after long-term infusion of thiopental exceeding 300 mg/kg body weight, the clearance of thiopental follows a zero-order kinetic [26], resulting in a prolonged elimination time as the blood values decrease. This, in turn, nearly doubles thiopental’s elimination half-life [10]. Based on an average elimination half-life of 24 h, thiopental as measured in CSF and serum is cleared after 6 and 9 days, respectively. This prolonged persistence of thiopental in CSF and serum correlates with the maximal concentrations measured in CSF and serum which is best explained by enzymatic saturation [26]. The shorter persistence of thiopental in CSF compared to serum is most likely due to the redistribution behavior of thiopental leaving the central compartment as the blood concentrations begin to decrease [23]. Since the CSF concentrations are in the range of 6–33% of corresponding serum levels, a moderate decline in serum will lower the CSF values below the detection limit once the thiopental infusion is stopped.

Changes in EEG after Barbiturate Coma

Prolonged persistence of thiopental in CSF and serum coincides with the long-term absence of responsiveness to exteroceptive stimuli for as long as 12 days after terminating thiopental infusion. This suggests that present but decreasing thiopental levels are still able to inhibit neuronal function. As the samples were collected once a day, the measurements do not allow estimating a threshold for CSF or serum thiopental needed to induce and reverse coma. However, if the threshold of 40 \(\mu g/ml\) as found to induce coma in a thiopental-free brain, can be transferred to the days following long-term thiopental infusion, EEG changes should be reversed once blood thiopental levels drop below 40 \(\mu g/ml\). Normal cortical responsiveness should, therefore, recur following the 2nd day after terminating thiopental infusion. The persisting loss of cerebral function, however, suggests altered neuronal susceptibility to thiopental after long-term administration or the generation of an active metabolite. Pentobarbital, the desulfured metabolite of thiopental, exerts comparable seda-
tive-hypnotic actions. Its average elimination half-life exceeds that of thiopental by 20 h [18]. Provided that this active metabolite has been generated during long-term infusion of thiopental, the prolonged loss in cortical activity and responsiveness could be due to pentobarbital once serum thiopental levels drop below 40 μg/ml. However, the presence of active metabolites inducing persisting loss of cortical activity remains to be demonstrated.

Theoretically, the calculated decline of thiopental in serum and the recurrence of cortical responsiveness to external stimuli could replace serial chemical analysis of thiopental after stopping its long-term infusion. This, however, requires measurement of maximal serum thiopental levels during the infusion period since they predominantly influence the persistence of thiopental and the prolonged absence of cortical responsiveness. Rapid and inexpensive analysis of thiopental in serum during and after its long-term administration helps to avoid miscalculation of the disappearance rate of thiopental with speculation concerning the observed delayed neurological recovery of these patients. The loss in cortical activity persisting in the early phase after barbiturate coma should not be mistaken as irreversible functional impairment or even cerebral damage. As shown in this study those patients with continuing loss of cortical responsiveness exceeding 5 days (No. 3, 4, 5, 8) have a moderate and good neurological outcome as assessed by their GOS 3–6 months after trauma (tables 1, 2).

Conclusions

Delayed neurological recovery in brain-injured patients is influenced by persisting thiopental levels in serum and CSF even if its administration has been terminated a week earlier. Therefore, quantitative analysis of thiopental at least in serum becomes indispensable in predicting the length of drug-induced neurological alteration after stopping long-term barbiturate infusion.

References

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