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Research Report

Thiopental exaggerates ischemic brain damage and neurological deficits after experimental stroke in spontaneously hypertensive rats

Yi-Fei Duan[a], Chang Liu[b], Yun-Feng Zhao[c], Wei-Ming Duan[d], Li-Ru Zhao[e,*]

[a]Freeman School of Business, Tulane University, New Orleans, LA, USA
[b]Rhodes College, Memphis, TN, USA
[c]Department of Pharmacology, Toxicology and Neuroscience, Louisiana State University Health Sciences Center, Shreveport, LA, USA
[d]Department of Cellular Biology and Anatomy, Louisiana State University Health Sciences Center, Shreveport, LA, USA
[e]Department of Neurology/Cellular Biology and Anatomy, Louisiana State University Health Science Center, 1501 Kings Highway, P.O. Box 33932 Shreveport, LA 71130-3932, USA

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ABSTRACT

Thiopental is an anesthetic used for controlling high intracranial pressure (ICP) caused by brain surgery, brain trauma, and severe stroke. However, it remains controversial whether Thiopental is detrimental or beneficial in ischemic stroke. In this study, we used an animal model of ischemic stroke in spontaneously hypertensive rats to determine whether or not Thiopental is neuroprotective in the setting of brain ischemia. We observed that Thiopental caused a prolonged duration of unconsciousness with a high rate of mortality, that Thiopental created exaggerated neurological deficits that were revealed through limb placement tests at 4 days and 4 weeks after brain ischemia, and that infarct volume was increased in Thiopental-anesthetized rats. These data suggest that Thiopental is detrimental in ischemic stroke. Thus, our findings raise a caution about the use of Thiopental in the setting of ischemic stroke.

1. Introduction

Thiopental, also known as Thiopental sodium, Pentothal, thiopentone, and trapanal, is a rapid-onset and short-acting barbiturate anesthetic. Thiopental has been shown to reduce intracranial pressure (ICP) through the reduction of cerebral oxygen consumption and decrease of cerebral blood flow (CBF) (Huynh et al., 2009; Turner et al., 2005). This drug has been used for more than 70 years as an anesthetic or a therapeutic coma inducer to control elevated ICP, which is caused by a variety of clinical conditions such as brain surgery, head trauma, or ischemic brain edema (Huynh et al., 2009; Schwab et al., 1997; Turner et al., 2005). Although in vitro studies have shown that Thiopental protects neurons against hypoxia (Wang et al., 1999) and nitric oxide-mediated neurotoxicity (Shibuta et al., 2000), the neuroprotective effects of Thiopental in stroke patients or in experimental stroke in laboratory animals remain controversial (Brain Resuscitation Clinical Trial I Study Group, 1986, Chen et al., 2003; Cole et al., 2001; Schmid-Elsaesser et al., 1999; Schwab et al., 1997). The aim of

* *Corresponding author*. Fax: +1 318 675 5889.
E-mail address: lzhao@lsuhsc.edu (L.-R. Zhao).

Abbreviations: BP, blood pressure; ICP, intracranial pressure; SHR, spontaneously hypertensive rat; CBF, cerebral blood flow; ANOVA, analysis of variance

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this study, therefore, is to determine whether Thiopental is beneficial or detrimental in ischemic brain damage.

2. Results

2.1. *Duration of unconsciousness was prolonged and mortality was increased by Thiopental*

The duration of unconsciousness differed greatly among the animals injected with each of the three anesthetics: Thiopental and two anesthetic controls, Equithesin and Methohexital. When compared to both Equithesin and Methohexital, Thiopental induced a significantly longer duration of unconsciousness ($p<0.01$) (Table 1). Methohexital causes the shortest duration of unconsciousness among the three groups ($p<0.01$). In addition, none of the rats in either the Equithesin or the Methohexital groups died after brain ischemia. However, 40% of rats were found dead in the group of Thiopental, suggesting there is a detrimental effect of Thiopental in brain ischemia.

2.2. *Neurological deficits were much more severe in the rats anesthetized with Thiopental*

Neurological deficits induced by cerebral cortical ischemia were evaluated with limb placement tests 4 days and 4 weeks after brain ischemia. We observed that the Thiopental-anesthetized rats 4 days post-ischemia obtained significantly lower scores than the rats anesthetized with Equithesin or Methohexital (Fig. 1) ($p<0.05$). In addition, 4 weeks after induction of brain ischemia, Thiopental-anesthetized rats again displayed significantly poor performance during the tests as compared with Equithesin- or Methohexital-anesthetized rats (Fig. 1) ($p<0.05$). These data indicate that Thiopental causes severe neurological deficits and poor functional recovery.

2.3. *Infarction size was increased by Thiopental*

In addition to cause of the severe neurological deficits, Thiopental anesthesia during brain ischemia resulted in a significantly enlarged infarct volume as compared to those in either Equithesin- or Methohexital-anesthetized rats (Fig. 2) ($p<0.01$). The total infarct volume in Thiopental-anesthetized rats was 31.98±2.69%, whereas the infarct volume was 11.12±2.45% in Equithesin-anesthetized rats and 13.86±1.94% in the rats anesthetized with Methohexital. This observation suggests that Thiopental increases neuron loss during brain ischemia.

Table 1 – Duration of unconsciousness after anesthesia.

Group	Mean (minutes)	SE
Thiopental	218.33 **	9.80
Equithesin	72.80 ##	5.42
Methohexital	32.89	1.48

** $p < 0.01$ compared to Equithesin and Methohexital.

$p < 0.01$ compared to Methohexital.

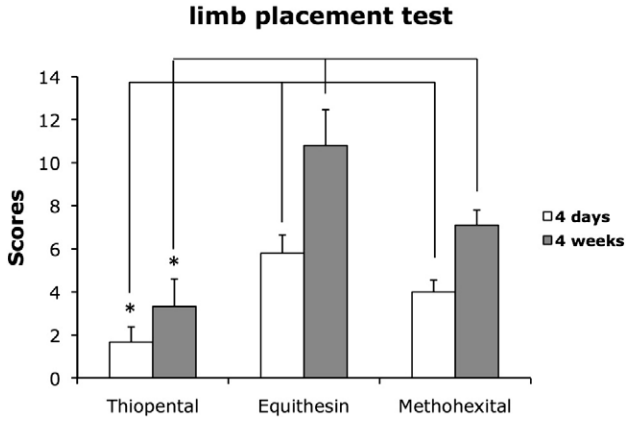

Fig. 1 – Evaluation of neurological deficits by limb placement test. Note that significantly poor performance during the test was observed in Thiopental-anesthetized rats at 4 days and 4 weeks after brain ischemia. Mean±SE. *$p<0.05$ compared to the rats in the groups of Equithesin and Methohexital.

3. Discussion

In the present study, we observed that Thiopental caused a long period of unconsciousness, a high mortality rate, an increase in infarct volume, and severe neurological deficits in a rat model of ischemic stroke. These results provide evidence of the detrimental effect of Thiopental on brain ischemia.

It has been a controversial issue concerning neuroprotective effects of anesthetics. Anesthetic agents, including barbiturates or inhalational anesthetics, have been shown to have neuroprotective effects in neuronal cultures and in the setting of global or focal cerebral ischemia. Therefore, it has been proposed that anesthetic agents can be used as preconditioning agents to prevent ischemic damage in the brain (Kitano et al., 2007). However, conflicting data and negative results do not support the use of anesthetic agents as neuroprotectants. Thus, whether or not anesthetics protect the brain from ischemic injury is a critical question to be answered. Recently, several excellent review articles have critically evaluated the research findings concerning the neuroprotective effects of anesthetic agents over the past four decades (Kitano et al., 2007; Koerner and Brambrink, 2006; Traystman, 2004). These reviewers revealed conflicting and inconsistent results among the anesthetic studies: some studies suggested a neuroprotective role of anesthetic agents in focal or global cerebral ischemia; other investigators failed to show any neuroprotective effects of these agents; some data even displayed neurotoxic effects. In fact, it appears that the effects of the anesthetic agents are very much dependent upon the animal model used for the studies, species, age or gender of the animals, dose and timing of intervention, and time for evaluation. Overall, based on these conflicting data it is difficult to draw any firm conclusion regarding the neuroprotective effects of anesthetics in brain ischemia.

In this study, we sought to determine whether or not Thiopental has neuroprotective effects in rat model of focal cerebral ischemia in SHRs; we chose Methohexital and Equithesin (containing 16.2% Pentobarbital) as controls.