


RESEARCH LETTER

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How to monitor thiopental administration in the intensive care unit for refractory status epilepticus or intracranial hypertension?

Erika Dabricot^{1†}, Inès Seqat^{2†}, Frédéric Dailier¹, Sylvain Rheims^{2,3}, Sebastien Boulogne^{2,3} and Baptiste Balança^{1,3*} 

Dear editor,

Thiopental continuous administration can be used as a rescue therapy for refractory status epilepticus (SE) or intracranial hypertension (IH). It induces an electroencephalographic (EEG) slowing up to a burst suppression state. The subsequent reduction in the cerebral metabolic demand and blood flow also allows decreasing the intracranial pressure (ICP) [1]. The continuous administration is usually guided both by thiopental serum concentration, to avoid accumulation, and efficacy on seizures or ICP. Thiopental side effects (hemodynamic dysfunction or immunosuppression) can occur at concentrations of 30–70 mg/ml [2, 3]. Conversely, the relation between serum concentrations and efficacy is less robust. In healthy subjects during anesthesia and in brain-injured patients, there is a great variability in the concentration needed to reach the same EEG changes [4, 5], with an overlap between the therapeutic and toxic ranges. The digitalization of the EEG signal provides quantitative indexes at the bedside and may allow tailoring sedative administration in the intensive care unit (ICU). For instance, the suppression ratio (SR) provides a metric of the depth of sedation during general anesthesia [5]. Since the target of thiopental sedation is to reach a discontinuous EEG activity (i.e., $SR \geq 10\%$); the aim of the herein

study was to evaluate the relationship between the thiopental concentration and the SR in patients with a refractory SE or IH.

We conducted a retrospective study (2013–2020) in adult patients sedated with thiopental and monitored with a continuous EEG, in the neurological ICU of the Hospices Civils de Lyon (France). We analyzed EEG signals of 2 h windows around the serum measurements (1 h before and after). Suppression periods were defined by an EEG amplitude $< 10 \mu V$ for ≥ 400 ms [6] and was calculated on 2 s epochs on the central derivation with the best signal (Fz-Cz or adjacent; BRAIN-QUICK, Micromed). We took the mean SR of the 2 h. The relation between concentration and duration of thiopental administration and the SR was analyzed with a linear mixed effect model with the R software (lme4 library). The diagnostic accuracy of thiopental concentration to predict a discontinuous EEG was analyzed with a receiver operating characteristic curve (ROC, pROC library). Data are presented as their median and interquartile range.

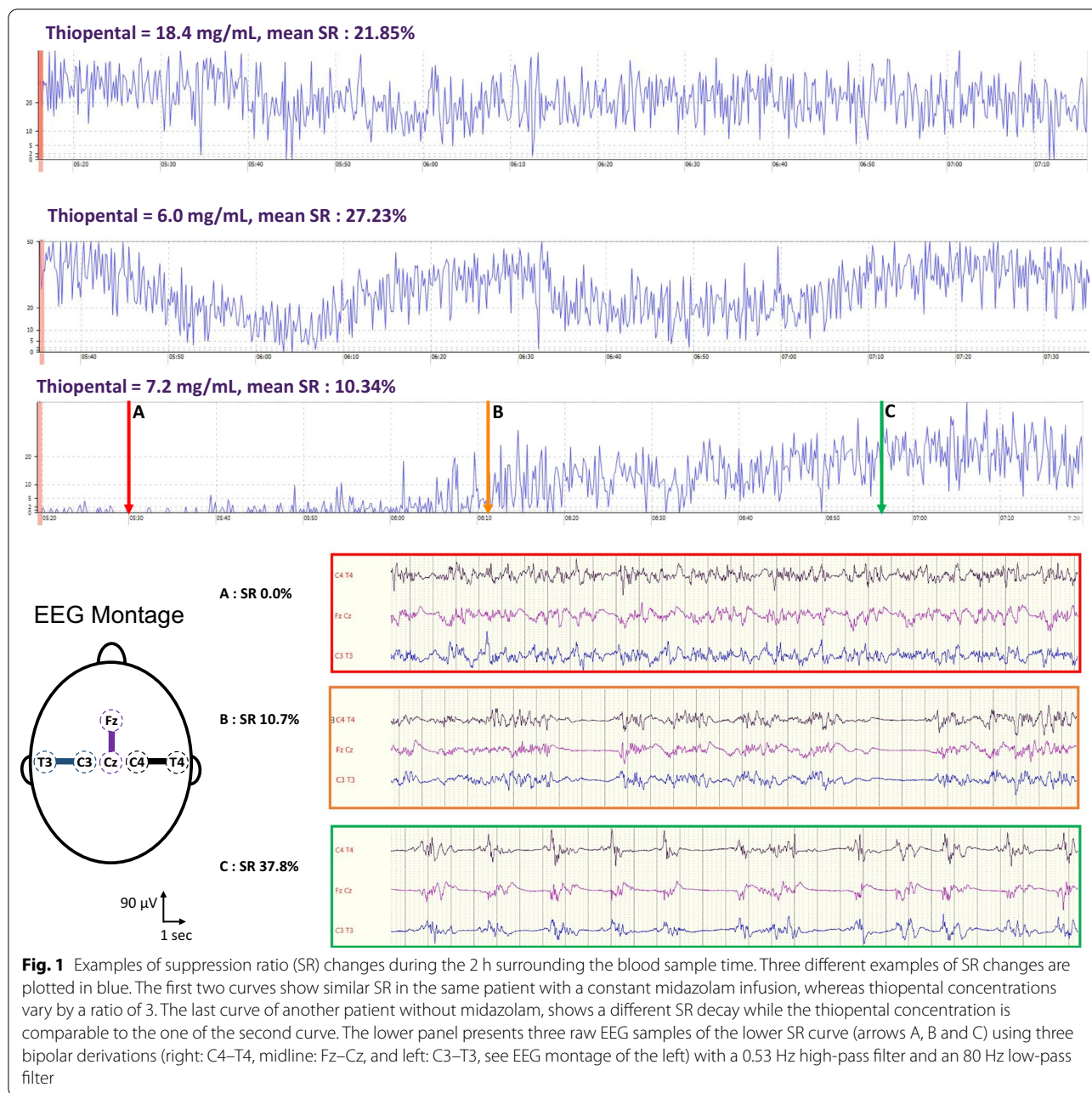
We included 30 patients, 47% ($n = 14/30$) had a refractory SE. They were 39.5 years old [27.5–55.5], 30% ($n = 9$) were female, and 37% had a potent thiopental adverse effect (sepsis: $n = 5$; hemodynamic instability: $n = 6$). The median concentration of thiopental ($n = 95$ samples) was 16.5 mg/ml [8.5–23.1], with a median administration rate of 2.1 mg/kg/h [1.3–2.9]. At the blood sampling time, 45.3% ($n = 43/95$) of the EEG were discontinuous with heterogeneous SR decay time (Fig. 1). 74% of the EEG from patients with a SE did not have epileptic discharges and 68% of patients with an

*Correspondence: baptiste.balanca@chu-lyon.fr

[†]Erika Dabricot and Inès Seqat have contributed equally to this work.

¹ Department of Neurological Anesthesiology and Intensive Care, Hospices Civils de Lyon, Hôpital Pierre Wertheimer, Groupement Hospitalier Est, 59 Boulevard Pinel, 69500 Bron, Lyon, France
Full list of author information is available at the end of the article

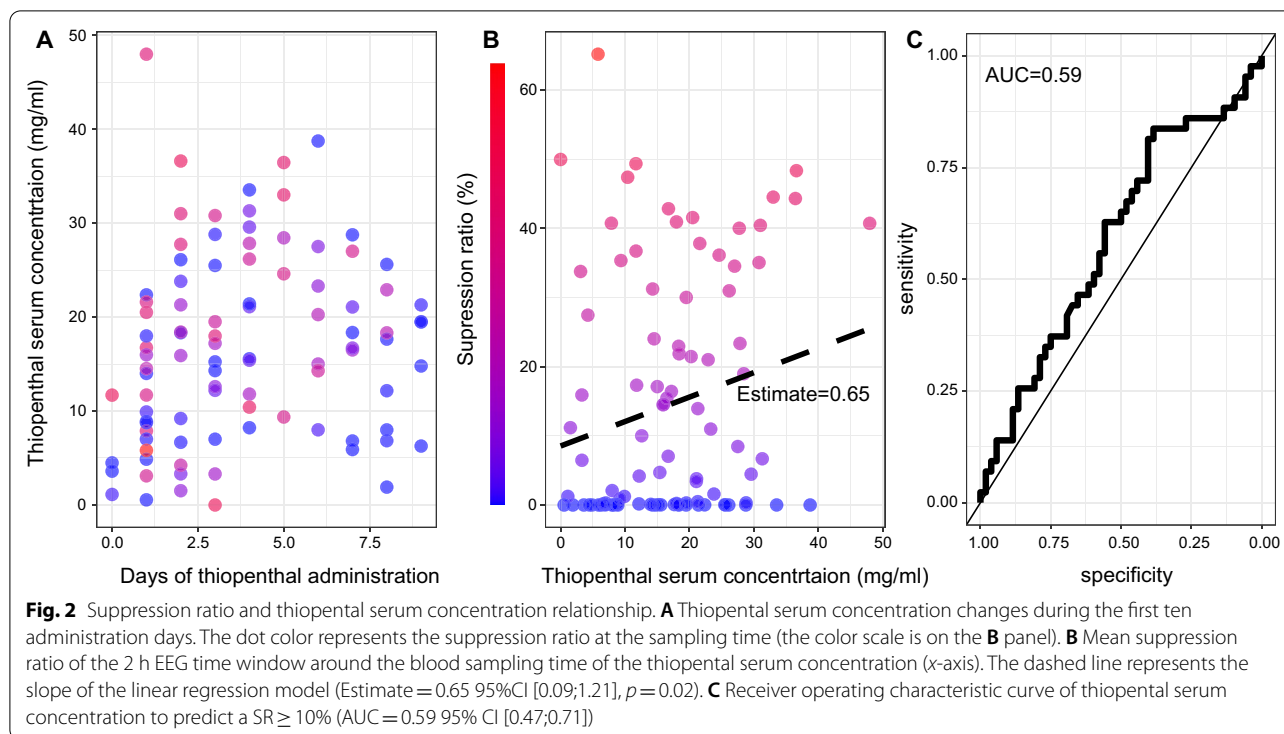




IH had an ICP < 25 mmHg. The ICP value was not significantly associated with the thiopental concentration. There was a significant association between thiopental concentration and SR, which was not dependent on the indication (SE or IH). However, for a given thiopental concentration, the level of SR was highly variable and thiopental concentration could not predict a discontinuous EEG (AUC of the ROC = 0.59 95%CI [0.47; 0.71], Fig. 2). Other sedative agents were also administered in

20 patients but did not significantly influence SR; their withdraw led to a SR decrease in 4 cases.

The main limitation of the herein study is its retrospective design. Given the heterogeneity of the EEG changes for a given thiopental administration, we would argue to have a continuous SR monitoring when using barbiturate to reach a discontinuous activity. The concomitant monitoring of electrophysiological data and serum concentration might help tailor the individual administration and monitor the effect of thiopental



on brain activity. Such strategy will need to be evaluated in a prospective trial.

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Authors' contributions

BB, ED, IS and SB conceived and design the study. ED collected the data from digital medical records. IS and SB reviewed electrophysiological data. BB analyzed the data. BB, ED, IS and SB interpreted the data. ED and BB draft the article. All authors critically revised the article. All authors approved the final version to be published.

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Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the French Intensive Care Society (No. IRB 00010254-2021-032).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Department of Neurological Anesthesiology and Intensive Care, Hospices Civils de Lyon, Hôpital Pierre Wertheimer, Groupement Hospitalier Est, 59 Boulevard Pinel, 69500 Bron, Lyon, France. ²Department of Functional

Neurology and Epileptology, Hospices Civils de Lyon and Lyon 1 University, Lyon, France. ³Lyon's Neuroscience Research Center, INSERM U1028/CNRS UMR 5292, Lyon 1 University, Lyon, France.

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