Technical Report

The precipitate formed by thiopentone and vecuronium

Takumi Taniguchi MD, Ken Yamamoto MD,
Tsutomu Kobayashi MD

***Purpose**: To determine the composition and solubility of the precipitate formed by thiopentone and vecuronium in vitro.*
***Methods**: The precipitate formed by mixing thiopentone 2.5% and vecuronium 0.1% at room temperature was analyzed by ultraviolet spectrophotometry and high performance liquid chromatography (HPLC). The solubility of the precipitate in human plasma was measured by HPLC.*
***Results**: The UV absorption spectrum of the precipitate resembled that of thiopentone. HPLC analysis produced a single peak with the same retention time as thiopentone (4.6 min). In human plasma the solubility of the precipitate was not different from that of thiopentone acid. The solubility of thiopentone was greater than that of the precipitate.*
***Conclusion**: The precipitate formed by thiopentone and vecuronium in vitro consisted of thiopentone acid, which was insoluble in human plasma.*

***Objectif**: Déterminer la composition et la solubilité du précipité formé par le thiopentone et le vécuronium in vitro.*
***Méthodes**: La précipité formé par le mélange de thiopentone 2,5% et de vécuronium 0,1% à la température de la pièce a été analysé par spectrométrie aux rayons ultraviolets et par chromatographie en phase liquide à haute performance (CPLH). Chez l'humain, la solubilité du précipité a été mesuré par CPHL.*
***Résultats**: L'absorption du spectre ultraviolet du précipité était identique à celle du thiopentone. L'analyse par CPLH produit un seul pic avec le même temps de rétention que le thiopentone (4,6 min). Dans le plasma humain, la solubilité du précipité de différait pas de celle de l'acide de thiopentone. La solubilité du thiopentone était plus grande que celle du précipité.*
***Conclusion**: La précipité formé par le thiopentone èt le vécuronium in vitro consistait en acide de thiopentone lequel est insoluble dans le plasma.*

Key words
ANAESTHETICS, INTRAVENOUS: thiopentone;
NEUROMUSCULAR RELAXANTS: vecuronium;
DRUG INTERACTIONS: thiopentone, vecuronium.

From the Department of Anesthesiology and Intensive Care Medicine, School of Medicine, Kanazawa University.
Address correspondence to: Dr. Takumi Taniguchi, Department of Anesthesiology and Intensive Care Medicine, School of Medicine, Kanazawa University, 13-1 Takara-machi, Kanazawa 920, Japan.
Phone: 81-762-62-8151. Fax: 81-762-34-4267.
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Thiopentone, a short-acting barbiturate, is often administered in conjunction with neuromuscular blocking agents such as vecuronium. When solutions of thiopentone and vecuronium are administered consecutively during the induction of anaesthesia, formation of a white precipitate has been observed at the interface of the two solutions. Intravenous tubing may be occluded by this precipitate. Formation of the precipitate may result in patient awareness with or without muscle relaxation. Morton *et al.*[1] identified the precipitate formed by thiopentone and pancuronium *in vitro* as thiopentone acid. However, they used only ultraviolet (UV) absorption spectrophotometry, and it was unclear whether the precipitate was soluble in human plasma. The object of this study was to elucidate the composition of the precipitate and to measure its solubility in human plasma.

Methods

A commercial preparation of 300 mg thiopentone sodium with 18 mg sodium carbonate (Ravonal™, Tanabe, Osaka, Japan) was diluted with 12 ml distilled water immediately before each study. Commercially supplied vecuronium (Masculax™, Organon, Oss, the Netherlands) was diluted with distilled water in 0.1% solution. A precipitate was prepared by mixing 4 ml thiopentone 2.5% (100 mg) and 4 ml vecuronium 0.1% (4 mg) at room temperature. The precipitate was centrifuged for ten minutes at 3500 × g rpm, washed twice with 20 ml distilled water and redissolved in 5 ml 0.1 N NaOH solution. Characteristics of the redissolved precipitate

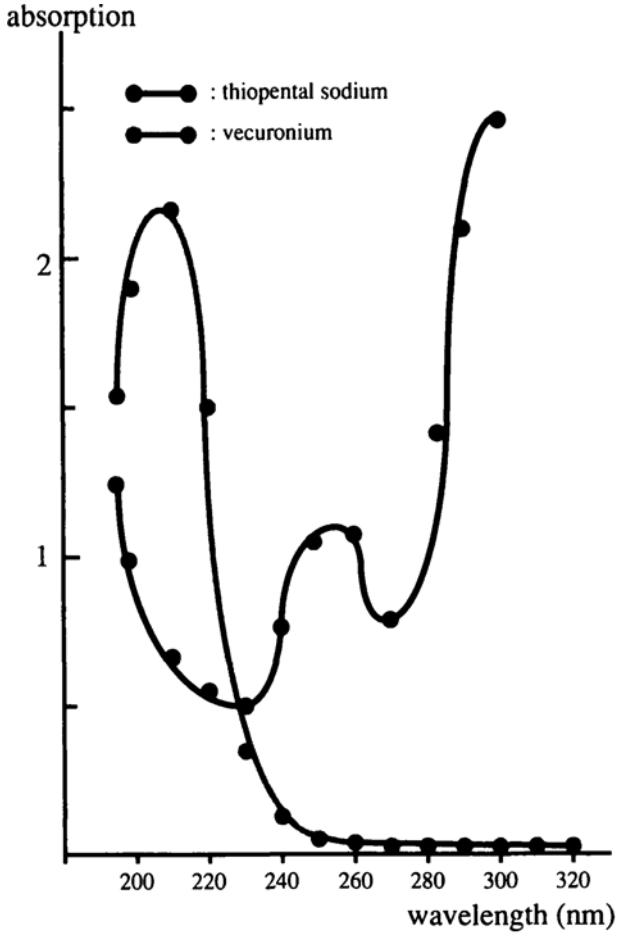

FIGURE 1 The ultraviolet (UV) light absorption spectrums of thiopental sodium and vecuronium bromide. The absorption peak of thiopental sodium is at 260 nm, and thiopental sodium strongly absorbs UV light at 300 nm. The absorption peak of vecuronium bromide is at 210 nm.

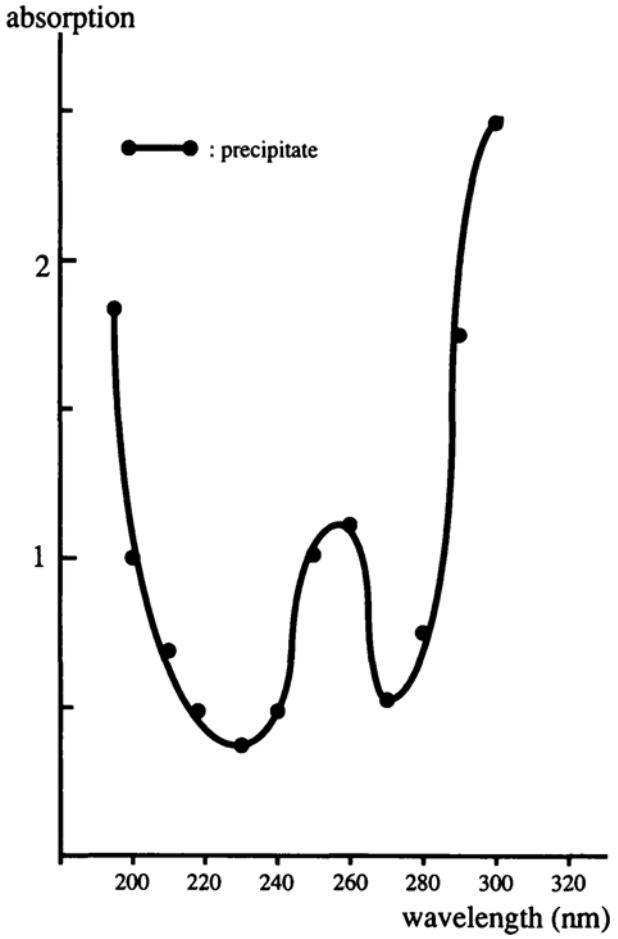

FIGURE 2 The ultraviolet (UV) light absorption spectrum of the precipitate. The absorption peak of the precipitate is at 260 nm, and the precipitate strongly absorbs UV light at 300 nm.

were determined by UV spectrophotometry and high performance liquid chromatography (HPLC). The UV absorption spectra (195–300 nm) of thiopentone and vecuronium were obtained using a Hitachi-Perkin-Elmer-139 spectrophotometer (Hitachi, Tokyo, Japan). HPLC analysis was performed according to the method of Blackman *et al.*[1] using a model ALC/GPC 204 chromatograph equipped with a fixed-wavelength absorbance detector (214 nm) and a μ BondaPack/C18 reversed-phase column (Waters, Milford, MA, USA). The mobilephase was a 40:60 mixture of acetonitrile-phosphate buffer at a flow rate of 2.0 $ml \cdot min^{-1}$.

The solubility of the precipitate, thiopentone acid and thiopentone in human plasma was determined by HPLC. Thiopentone, thiopentone acid or the precipitate was dissolved in 3 ml human plasma at 37°C. The thiopentone acid/plasma sample (0.5 ml) was added to 2 ml ethanol. The mixture was then centrifuged for ten minutes at 3000 × g rpm. A 50 μl of the supernatant was injected into the HPLC. A linear standard curve was obtained for thiopentone concentrations of 0.5–1000 $\mu g \cdot ml^{-1}$ of plasma/ethanol. The minimum sensitivity was 0.5 $\mu g \cdot ml^{-1}$ of plasma/ethanol.

Results are expressed as means ± SD. Data of the solubility of the precipitate and of thiopentone acid were compared using an unpaired t test. A level of $P < 0.05$ was considered to be statistically significant.

Results

The UV absorption spectrum of thiopentone includes a well-separated peak at 260 nm. Thiopentone strongly absorbed UV light at 300 nm (Figure 1). Vecuronium showed a maximum peak at 210 nm and did not absorb UV light at 300 nm. The absorption maximum for the

precipitate was at 260 nm. The precipitate strongly absorbed UV light at 300 nm and did not have a peak at 210 nm (Figure 2). The HPLC analysis produced a single peak for thiopentone and for the precipitate. The same retention time was observed for thiopentone and the precipitate (4.6 min).

In human plasma, the solubility of the precipitate (337 ± 17 $\mu g \cdot ml^{-1}$) was not different from the solubility of thiopentone acid (355 ± 24 $\mu g \cdot ml^{-1}$). However, the solubility of thiopentone was greater (>100 $mg \cdot ml^{-1}$).

Discussion

The present study showed that the precipitate formed by thiopentone and vecuronium is insoluble in human plasma and is probably composed entirely of thiopentone acid.

Morton *et al.*[1] identified the precipitate formed by thiopentone and pancuronium *in vitro* as thiopentone acid by UV spectrophotometry. The spectrophotometric data from the present study is in agreement with Morton *et al.*, and is farther supported by HPLC analysis. The UV absorption spectrum of the precipitate was nearly identical to that of thiopentone and different from that of vecuronium. The HPLC analysis revealed a single peak for the precipitate that had the same retention time as thiopentone. These results suggest that the precipitate did not contain a combination of thiopentone and vecuronium.

The precipitate and thiopentone acid have a similar solubility in human plasma. Both substances were considerably less soluble than thiopentone. The solubility of thiopentone in water is 700 $mg \cdot ml^{-1}$, but that of thiopentone acid is <0.1 $mg \cdot ml^{-1}$ in water.[3] Results of this study indicate that the precipitate is insoluble in human plasma as well as in water. The low solubility suggests that if the precipitate enters the venous circulation, it may block the narrow blood vessels, perhaps resulting in adverse effects such as pulmonary infarction.

This study analyzed the composition and solubility of the precipitate *in vitro*. Although we did not study the effect of precipitate formation on drug potency or on the risk of vascular occlusion *in vivo*, our observations indicated that administration of the drugs in a manner that leads to precipitate formation should be avoided.

In summary, the precipitate formed by thiopentone and vecuronium *in vitro* consisted of thiopentone acid which was insoluble in human plasma. To avoid the formation of such a precipitate in the clinical setting, the intravenous tubing should be thoroughly flushed after administration of each drug. If a precipitate forms in the tubing, it should be removed before it can enter the circulation.

Acknowledgement

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References

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