Technical Report

The effect of pancuronium on the solubility of aqueous thiopentone

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In this study we identified the precipitate formed when pancuronium bromide (pH 3.9) and sodium thiopentone (pH 10.6) are combined in vitro. *A precipitate formed when sufficient pancuronium was added to thiopentone to decrease the pH below 9.25. The precipitate was isolated, redissolved in alkaline solution and identified as thiopentone using ultraviolet spectrophotometry. Pancuronium was soluble in water in the pH range of 2.0 to 12.0, whereas thiopentone was soluble in water only at a pH greater than 9.90. We conclude that thiopentone precipitates when combined with pancuronium because of a pH-dependent decrease in the solubility of thiopentone, rather than a chemical interaction.*

When solutions of sodium thiopentone and pancuronium bromide are combined, a flocculent white precipitate forms.[1] This precipitate can occlude an intravenous catheter during the induction of anaesthesia. If pancuronium is administered before thiopentone, the resultant precipitate may occlude the intravenous catheter before an adequate dose of thiopentone is administered. This may result in patient awareness and recall. Induction techniques requiring the rapid administration of pancuronium and thiopentone (as in patients with full stomachs and open eye injuries) must therefore include a thorough flush of the intravenous tubing after administration of each drug.[2] If the precipitate is administered, its effects on drug potency, pulmonary vascular tone or the incidence of peripheral thrombophlebitis are unclear.

Since a number of reaction products could result from combining solutions of thiopentone and pancuronium, we determined the composition of the precipitate and supernatant when these two drugs are combined.

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

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Methods

A commercial preparation (Abbott Laboratories) of 1 g of sodium thiopentone with 60 mg sodium carbonate was diluted with 40 ml of double-distilled water immediately before each study. Commercially supplied ampoules of pancuronium bromide in a 0.1 per cent solution (Organon) were warmed to room temperature for all experiments.

To determine the effect of pH on the solubility of thiopentone, 10 ml of thiopentone (2.5 per cent) was stirred continuously at room temperature while the pH was monitored using a Radiometer pH meter. The pH meter was calibrated with three standard solutions of pH 4.01, 7.00, and 9.18. Hydrochloric acid (HCl) (0.2 N) was titrated slowly into the thiopentone solution. When a persistent white suspension was observed, the pH was recorded. The study was then repeated with pancuronium 0.1 per cent substituted for the 0.2 N HCl. All titrations were repeated in triplicate.

Ultraviolet (UV) light is strongly absorbed by covalent chemical bonds. A given arrangement of bonds (for example, a benzene ring) will absorb a specific range of UV frequencies within the UV spectrum. As a result, a complex molecule such as pancuronium or thiopentone will have a pattern of UV absorption which reflects its unique chemical structure. The UV absorption spectrum of thiopentone was determined by acidifying 2.5 per cent thiopentone with 0.1 N HCl. The resultant precipitate was washed, redissolved in NaOH solution, and analyzed. The UV absorption spectrum of pancuronium was determined after dilution to a 0.01 per cent solution.

In the final study, we analyzed the precipitate. A high-speed centrifuge tube was filled with 50 μl of 2.5 per cent thiopentone and 4.5 cc of 0.1 per cent pancuronium.

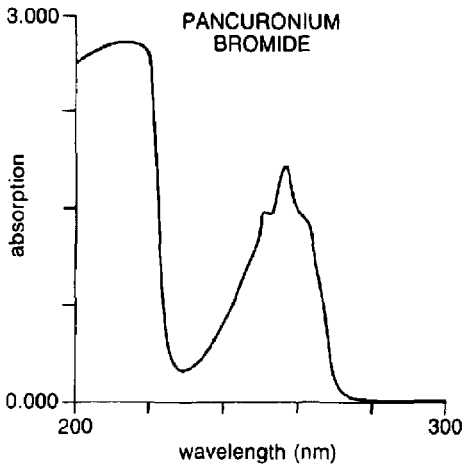

FIGURE 1 The UV absorption spectrum of pancuronium bromide in a 0.01 per cent solution. The absorption peak is at 256.5 nm.

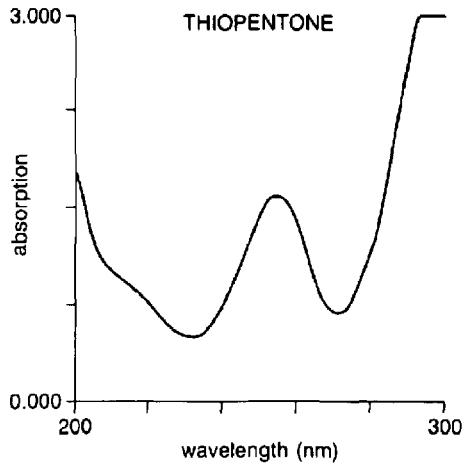

FIGURE 2 The UV absorption spectrum of sodium thiopentone in a 0.005 per cent solution. A solution of 2.5 per cent thiopentone was first acidified, and the resultant precipitate redissolved in a dilute alkaline solution. The absorption peak is at 254.5 nm.

Following centrifugation, the precipitate was washed with distilled water, redissolved in NaOH solution and analyzed by UV spectrophotometry. A Beckman DU-7 UV spectrophotometer was calibrated with double-distilled water before analysis of the samples.

Results

Thiopentone formed a cloudy precipitate at a pH of 9.90 ± 0.05 when titrated with 0.2 N HCl. Thiopentone titrated with pancuronium formed a precipitate at a pH of 9.25 ± 0.05.

The UV absorption spectrum of pancuronium is characterized by a well-defined peak at 256.5 nm which is bracketed by two shoulders (Figure 1). The absorption peak for thiopentone is at 254.4 nm, with two gradually tapering valleys toward each side of the peak (Figure 2). Thiopentone also absorbs UV light at 300 nm, whereas pancuronium does not.

When the precipitate from the mixture of thiopentone and pancuronium was redissolved in dilute alkaline solution, the UV absorption spectrum was characteristic of thiopentone (Figure 3). The UV absorption of the supernatant was characteristic of pancuronium (Figure 4). In replicate experiments, the additional small shoulder seen from wavelengths 280 to 290 nm was present in all samples of supernatant but not in the pancuronium control tubes.

Discussion

When solutions of thiopentone and pancuronium are combined, a white suspension of thiopentone forms if the pH of the resultant mixture is less than 9.25. Sodium thiopentone is soluble in water only at an alkaline pH ($pH > 9.90$). These observations indicate that thiopentone precipitates when it is combined with sufficient

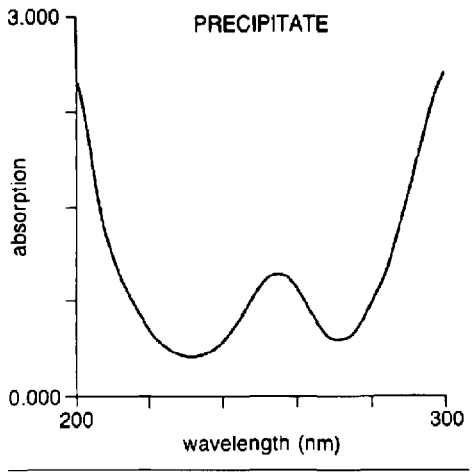

FIGURE 3 The UV absorption spectrum of the precipitate from a mixture of pancuronium bromide and sodium thiopentone. The precipitate was redissolved in a dilute alkaline solution. The absorption peak is at 255.0 nm.

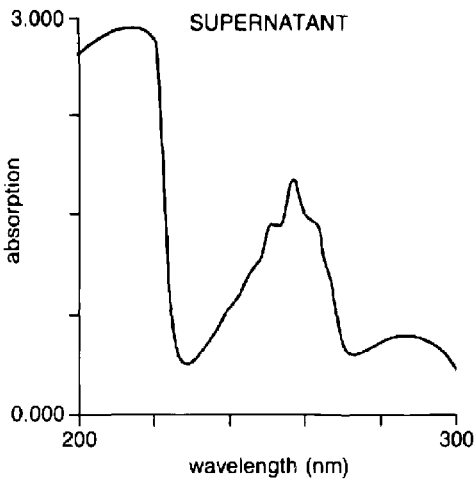

FIGURE 4 The UV absorption spectrum of the supernatant from a mixture of pancuronium bromide and sodium thiopentone. The supernatant was diluted ten-fold for spectrophotometry. The absorption peak is at 256.5 nm.

pancuronium to reduce the pH to less than 9.25. The small shoulder observed between wavelengths 280 and 290 nm (Figure 3) may be due to trace amounts of an acid-soluble pancuronium-thiopentone complex ion. Acid-soluble species could also explain our finding that thiopentone was soluble at a pH $\geqq$ 9.25 when titrated with pancuronium 0.1 per cent but was soluble only at a pH $\geqq$ 9.90 when titrated with 0.2 N HCl.

In summary, insoluble thiopentone is the precipitate formed when aqueous thiopentone is mixed with pancuronium. The principle clinical risk of inadvertently mixing thiopentone and pancuronium is the resultant loss of intravenous access. This is particularly likely with the small diameter catheters used in paediatric practice. To avoid this problem, we recommend a thorough flush of the intravenous tubing including the injection port after administration of each drug.

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References

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Résumé

Dans cette étude on a identifié le précipité qui se forme à la suite de la combinaison in vitro *du bromure de pancuronium (pH 3.9) et du thiopentone de sodium (pH 10.6). Si la quantité de pancuronium est suffisante, un précipité se forme lorsque le pH est en bas de 9.25. Le précipité était isolé, redissout dans une solution alcaline et identifié par spectophotométrie aux rayons ultraviolet comme étant le thiopentone. On a trouvé que le pancuronium était soluble dans l'eau lorsque le pH est aux alentours de 2.0 à 12.0, le thiopentone lui était soluble dans l'eau uniquement à un pH supérieur à 9.90. On conclut que le thiopentone précipite si combiné au pancuronium à cause de la diminution de solubilité du thiopentone qui est relié au pH plutôt qu'à une intéraction chimique.*