Evaluation of Histamine-releasing Property of Propofol in Whole Blood *in Vitro*

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We examined the property of emulsion form of propofol (ICI 35 868) to release histamine in whole blood *in vitro*. Heparinized whole blood from 10 healthy volunteers were incubated with medium and propofol at the final concentration of 0, 1, 10 and 100 $\mu g \cdot ml^{-1}$. The concentration of histamine in supernatant fluid after incubation was measured by radioimmunoassay. Histamine release was expressed as the percentage of the concentration of histamine released into supernatant fluid relative to the total cellualr histamine content, which was yielded by destroying cell components in the whole blood. Histamine release in the presence of propofol at the concentrations of 1, 10 and 100 $\mu g \cdot ml^{-1}$ were almost the same as histamine release in the absence of propofol. We conclude that emulsion form of propofol has no property to release histamine in whole blood *in vitro*. (Key words: propofol, intravenous anesthetic, histamine, whole blood, *in vitro*)

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Incidence of anaphylactoid reactions occurring during anesthesia is one per 5,000–20,000 of general anesthesia[1]. The reaction is mediated through non-immunological or immunological mechanisms. Direct histamine release is most commonly caused by non-immunological mechanisms[2]. Recently propofol has been used widely as an intravenous anesthetic[3–5]. Initially it was prepared as a 1% solution in Cremophor EL, which was reported to produce anaphylactoid reaction mediated by direct histamine release[6], and then this formation was withdrawn from clinical use. At the present time, propofol is prepared as emulsion form of 1% w/v solution in 10% soya bean oil, 2.25% glycerol and 1.2% purified egg phosphatide.

Withington[7] reported that propofol has no histamine release from basophils *in vitro*. However, allergic reaction *in vivo* depends on the balance among other factors such as blocking antibodies, the ability of basophils or mast cells to release other mediators. Therefore, we examined the property of the emulsion form of propofol to release histamine in whole blood *in vitro*.

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Materials and Methods

Preparation of supernatant fluid for histamine assay

Blood samples were taken from 10 healthy volunteers with an age range of 25 to 34 years who had no allergic disease and gave informed consent to the study which was approved

Table. Percentage of histamine released in the whole blood provocated with propofol *in vitro*

Concentration of propofol ($\mu g \cdot ml^{-1}$)	Histamine release (%)
0	1.4 ± 0.26
1	1.5 ± 0.50
10	1.5 ± 0.39
100	2.1 ± 0.48

histamine release (%) = E/C×100, where E is the histamine concentration in the supernatant fluid of the whole blood incubated in the presence or the absence of propofol, and C is the total cellular histamine concentration in the supernatant fluid of the whole blood in which cell components were destroyed by perchloric acid.

by the Local Ethics Committee. The supernatant fluid for the histamine assay was prepared by a modified method of Siraganian and Hook's[8]. Ten ml of whole blood was heparinized and diluted with 2.5 ml of PIPES buffered medium (piperazine-N, N'-bis 2-ethanesulforic acid, Wako Pure Chemical Industries, LTD, Osaka, Japan) containing 1 mM Ca^{+}, 0.5 mM Mg^{2+} and human serum albumin (Baxter Healthcare Corporation, Glendale, California, USA) (PIPES ACM). A 0.5-ml amount of propofol diluted with phosphate buffered salt (0.15 M, PH 7.6) which contained each final concentration of 1, 10 and 100 $\mu g \cdot ml^{-1}$ of propofol was put into the three plastic tubes (12 by 75 mm, Falcon No.2003, Becton Dickinson, Lincoln Park, New Jersey, USA) in an ice bath, and 0.5-ml medium (PIPES AMC) alone was put in the other tube in the same ice bath to measure spontaneous histamine released from whole blood in the absence of propofol. Then 0.5 ml of the diluted blood was added to all the tubes and these tubes in racks were transferred to a 37°C bath. These solutions were mixed by shaking the racks and incubated at 37°C for 60 min. Incubation of the solutions were stopped by cooling the tubes in an ice bath. To destroy all the cell components and measue the total cellular histamine content in the whole blood, 0.5 ml of 0.5% perchloric acid (Wako Pure Chemical Industries, LTD, Osaka, Japan) was added to the tube containing 0.5 ml of the diluted blood without propofol. It was centrifuged at 1200 × g for 30 min at 4°C. All experiments were performed in triplicate. The supernatant fluid was stored at −80°C till histamine assay.

Histamine assay

Histamine assay was performed by using HISTAMINE RADIOIMMUNOASSAY KIT® (Immunotech S.A., France, Eiken, Tokyo). The results were expressed as the percentage of the concentration of histamine released into the supernatant relative to the total cellular histamine content. The percentage of histamine released in the whole blood was calculated by using the following formula: histamine release (%) = E/C × 100, where E is the histamine concentration in the supernatant fluid of the whole blood incubated in the presence or the absence of propofol, and C is the total cellular histamine concentration in the supernatant fluid of the whole blood in which cell components were destroyed by perchloric acid.

Statistical analysis

Data are presented as mean ± SD. The statistical analysis was performed by using one-way analysis of variance (ANOVA), followed by Dunnett t for paired data. $P < 0.05$ was taken as statistically significant.

Results

Histamine release (%) in the presence of 1 $\mu g \cdot ml^{-1}$, 10 $\mu g \cdot ml^{-1}$ and 100 $\mu g \cdot ml^{-1}$ of propofol was not significantly higher than that in the absence of propofol (table).

Discussion

Anesthetics cause direct histamine release from circulating basophils and some population of mast cells[2]. Basophil histamine-releasing studies have been used in the investigation of adverse reaction to anesthetic agents[9-10]. Withington[7] reported that propofol does not release histamine from basophil *in vitro*. However, in anaphylactoid reactions to intravenous anesthetics, plasma histamine is not only directly released from basophils or mast cells but also by a consequence of antibody or complement involvement[11]. Therefore, measurement of histamine released into supernatant fluid from whole blood may be a better reflection of true *in vivo* situation compared with histamine liberation from basophil alone[8]. Thus, we used the diluted whole blood instead of basophils to examine the histamine-relasing property of propofol *in vitro*.

The result of this study demonstrated that propofol up to the concentration of 100 $\mu g \cdot ml^{-1}$ did not release histamine from whole blood *in vitro*. Required doses of propofol for induction of anesthesia in adults are normally 2 to 2.5 $mg \cdot kg^{-1}$, which produce plasma propofol concentration between 5 $\mu g \cdot ml^{-1}$ and 10 $\mu g \cdot ml^{-1}$ [4]. The concentration of 100 $\mu g \cdot ml^{-1}$ of propofol used in this study was 10 to 20 times of the concentration of clinical doses of propofol. This suggests that accidental overdose of propofol may not present problems with regard to histamine release from whole blood. Similar results have been reported by several authors[11-14].

Although propofol is thought to be a safe intravenous anesthetic with regard to direct histamine-liberation, 2 cases with adverse reactions caused by propofol have been reported; in one case IgE-mediated anaphylaxis was induced by propofol[15-16] and in another case anaphylactoid reaction was induced by propofol-atracurium[17]. It is possible that propofol which has no property of direct histamine release could induce anaphylaxis or anaphylactoid reaction. IgE-mediated anaphylaxis is obviously induced by mechanisms different from direct histamine release. In the anaphylactoid case with propofol-atracurium[17] rapid administration of these drugs is likely to be a cause of histamine release. Muscle relaxants such as vecuronium and pancuronium which have poor hisitamine-releasing property rarely cause severe clinical anaphylaxis, though there is a poor correlation between the histamine-releasing properties of drugs and their likelihood of producing a severe adverse reaction[2]. Consequently, propofol as well as any other drugs with poor histamine releasing properties should be used with caution in any patient with the likelihood of anaphylaxis.

In conclusion, the emulsion form of propofol has no property to release histamine in whole blood *in vitro*.

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