# Plasma Histamine Levels during Induction of Anesthesia with Propofol in Dogs

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We examined a property of emulsion formation of propofol (ICI 35868) to release histamine into circulating plasma in dogs. Plasma histamine was measured with radioimmunoassay before (baseline), and 1, 5 and 10 min after the administration of 15 mg·kg$^{-1}$ propofol. There were no significant differences between the plasma histamine levels at 1, 5 and 10 min after the administration of propofol and the baseline level. We conclude that the emulsion formation of propofol of 15 mg·kg$^{-1}$ does not release histamine during induction of anesthesia in dogs. (Key words: propofol, dog, histamine, intravenous anaesthetic)

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Incidence of anaphylactoid reactions occurring during anesthesia is one operation per 5,000–20,000 episodes of general anesthesia[1]. These reactions were mediated via non-immunoligical or immunological mechanisms. Non-immunological mechanism is commonly realted to direct histamine release[2]. Recently propofol (ICI 35868) has been widely used as an induction anaesthetic[3,4,5]. Initially it was prepared as a 1% solution in Cremophor EL, which have been reported to produce anaphylactoid reaction mediated by histamine release[6], and then this formation was withdrawn from clinical use. Propofol was therefore reformed as a 1% w/v solution in an aqueous emulsion consisting of 10% soya bean oil, 2.25% glycerol and 1.2% purified egg phosphatide. We evaluated a property of this emulsion formation of propofol to release histamine into circulating plasma during induction of anesthesia in dogs.

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## Materials and Methods

Seven mongrel dogs (12–23 kg body weight) were used. Approval was obtained from the institutional committee on animal investigations. Venous blood were taken through a catheter placed in a vein of the forearm before (baseline), and 1, 5 and 10 min after the administration of propofol of 15 mg·kg$^{-1}$, given over 30 sec. The blood was transferred immediately into an iced tube containing ethylenediaminetetraacetic acid (EDTA, 2Na), and centrifuged at 1200g for 30 min at 4°C. The plasma obtained was refrigerated at −80°C until histamine was assayed. The plasma histamine levels were measured by raidioimmunoassay, using HISTAMINE RADIOIMMUNOASSAY KIT® (Immunotech S.A. Marseille, France, Eiken, Tokyo).

The statistical analysis was performed by using one-way analysis of variance (ANOVA), followed by Fisher

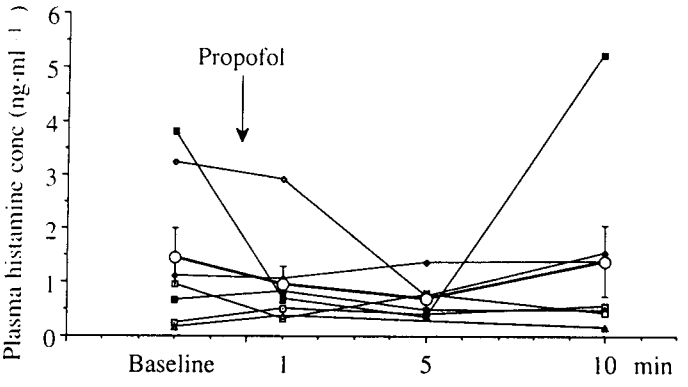


**Fig. 1.** Plasma histamine concentration ($ng \cdot ml^{-1}$) before and 1, 5, 10 min after administration of propofol of 15 $mg \cdot kg^{-1}$ in dogs.

Open circles and vertical lines represent mean and SE, respectively.

PLSD test for paired data. A $P$ values of $< 0.05$ was considered statistically significant.

## Results

Changes in plasma histamine concentrations before and 1, 5 10 min after the administration of propofol in each dog and means with standard errors are shown in figure 1. Plasma histamine levels at 1, 5 and 10 min showed no significant differences compared with the level of baseline in mean values of 7 dogs. There were no significant differences among the means measured at 4 periods of time.

## Discussion

Histamine is very easily released from blood cells into plasma during preparations for the histamine assay[7]. We withdrew venous blood and handled it extemely carefully to exclude mechanical release of histamine. The radioimmunoassay used in the present study can detect the plasma histamine level of 0.1 $ng \cdot ml^{-1}$. This is more sensitive than radioenzymatic assay used in the earlier studies on plasma histamine after the propofol administration[9,10,11].

The plasma histamine concentration did not increase at least for 15 min after the administration of propofol compared with baseline. Only one dog showed high plasma histamine levels before and 10 min after the administration of propofol. These two high levels probably included mechanically-released histamine, because the levels at 1 and 5 min remained low.

Our results revealed that propofol did not induce direct histamine release after the administration of propofol of 15 $mg \cdot kg^{-1}$. Glen and Hunter also reported that histamine concentration remained at a baseline value of 12–17 $ng \cdot ml^{-1}$ for 20 min in dogs given the emulsion formation of propofol (ICI 35868)[9]. The administered doses in this study was 6 to 7.5 times as large as induction dose required in human adults, usually 2 to 2.5 $mg \cdot kg^{-1}$ [4], and a dog is more susceptible to Cremophor, which has the direct histamine-releasing property than a man, pig or rabbit[12]. Therefore, it is less likely that the emulsion formation of propofol (ICI 35868) may produce direct histamine release in man. The evidence that propofol did not increase histamine levels *in vivo* and *in vitro* are proved by other authors[9–11,13–15].

The patient with thiopentone anaphylaxis has been reported to be inducted safely with propofol[16]. Although in clinical and experimental study propofol is thought to be a safe induction anaesthetic in regard to direct histamine-release, 2 cases with IgE-mediated anaphylaxis induced by propofol[17,18] and anaphylactoid reaction induced by propofol-atracurium[19]

are reported. It is possible that anaphylaxis or anaphylactoid reaction to even propofol without property of direct histamine release would occur. Because muscle relaxants such as vecuronium and pancuronium which have a poor histamine-releasing property rarely cause severe clinical anaphylaxis, there is a poor correlation between the histamine-releasing properties of drugs and their likelihood of producing a severe adverse reaction[2]. Therefore, propofol as well as any other drug without the histamine-releasing property should be administered in condideration of the likelihood of anaphylaxis or anaphylactoid reaction.

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