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EXPERIMENTAL

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Effect of propofol on adhesion of activated platelets to leukocytes in human whole blood

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Abstract *Objective:* To investigate the effect of propofol and its solvent Intralipid on the adhesion of activated platelets to leukocytes in vitro. *Design and setting:* Prospective study in an experimental laboratory. *Participants:* Sixteen healthy volunteers. *Interventions:* Whole blood was incubated for 60 min with propofol (4, 40 μg/ml), an equal volume of Intralipid 10% or phosphate-buffered saline (PBS). After stimulation with adenosine-5-diphosphate (ADP) platelet–leukocyte adhesion and platelet surface expression of P-selectin, GPIb and fibrinogen-binding to platelets were evaluated by flow cytometry. *Measurements and results:* The 4 μg/ml concentration of propofol did not alter binding of platelets to leukocytes, expression of P-selectin, GPIb and fibrinogen binding to platelets. The 40 μg/ml concentration of propofol reduced spontaneous and ADP-induced formation of platelet–neutrophil conjugates compared with PBS and the equal volume of Intralipid. In addition, binding of ADP-activated platelets to monocytes were also inhibited by 40 μg/ml propofol. Following incubation with propofol, platelets showed reduced binding of fibrinogen in the unstimulated and ADP-stimulated blood samples as well as a lower percentage of platelets with bound fibrinogen. Effects dependent on the solvent Intralipid were enhanced adhesion of platelets to monocytes in comparison with propofol (40 μg/ml) and PBS. *Conclusion:* In clinically used concentrations, propofol does not alter the adhesion of platelets to leukocytes in vitro. At ten-fold anesthetic concentration propofol reduced the formation of platelet–neutrophil and platelet–monocyte conjugates. We suggest that this effect is due to an inhibition of fibrinogen-binding to platelets by propofol. These effects were all independent of the propofol carrier Intralipid.

Keywords Propofol · Intralipid · Platelet–leukocyte conjugates · Inflammation

Introduction

Evidence suggests that activated platelets are closely involved in the regulation of inflammation, hemostasis, and thrombosis. Furthermore, interaction of platelets with leukocytes and endothelium may contribute to the pathogenesis of local and systemic inflammation processes. It is well established that platelets modulate leukocyte function upon direct adhesion primarily via an interaction between P-selectin on the platelet surface and P-selectin ligand (PSGL-1) on the surface of leukocytes [1, 2] as well as by soluble mediators [3]. In addition, adhesion of platelets to leukocytes seems not only to be an in vitro phenomenon, since increased platelet–leukocyte conjugates have been reported in sepsis [4], myocardial infarction [5], postischemic reperfusion damage [6], and thrombosis [7].

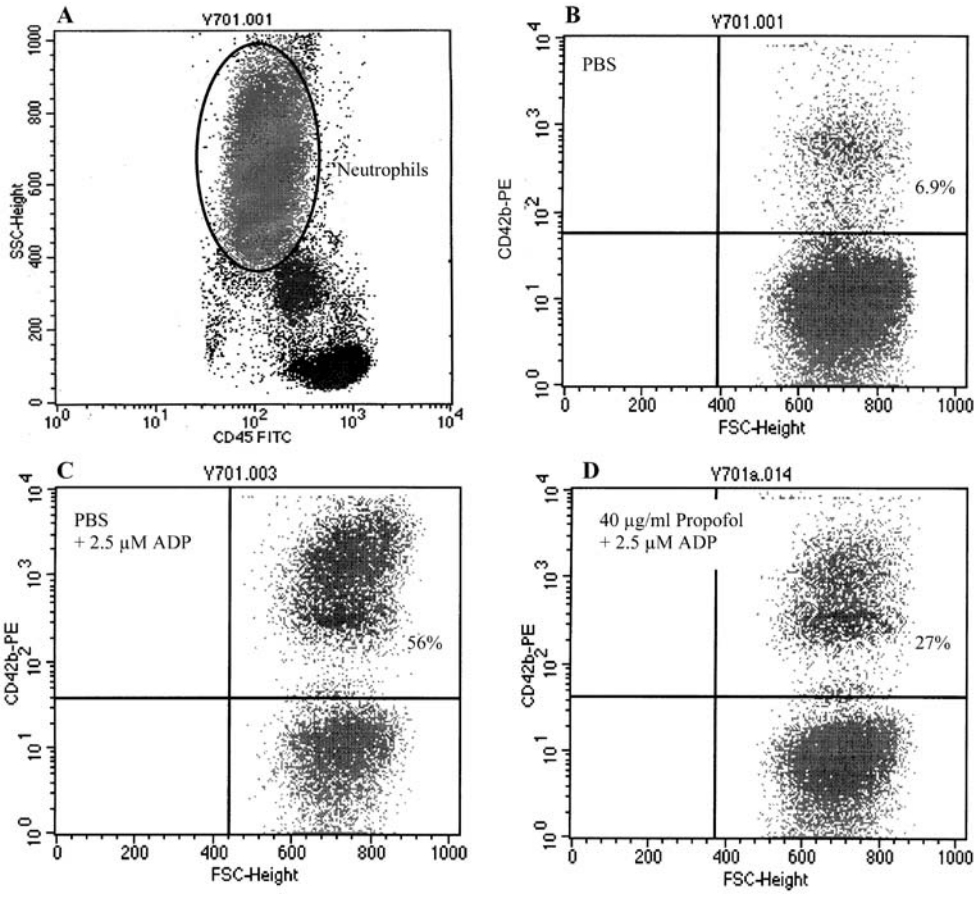

Fig. 1A–D Adjustment of the aquisition dot plots for analysis of the percentage of neutrophils with bound platelets. Neutrophils were identified in the sideward scatter (SSC) as well as their specific binding characteristics of anti-CD45-FITC (FL 1) as acquired on the flow cytometer (**A**). The events in the neutrophil gate above the horizontal line in the right upper quadrant (**B**) were considered to represent neutrophil–platelet conjugates and those below the line were considered to be platelet-free neutrophils, as determined by isotype control. **C** and **D** show a representative result of the inhibiting effect of 40 µg/ml propofol on the binding of ADP-activated platelets to neutrophils in comparison with PBS control

Anesthetic agents such as propofol are frequently used for sedation of critically ill patients. The effect of propofol on the cellular function of various types of leukocytes has been intensively investigated over the last years [8]. Most studies have been performed with isolated neutrophils or monocytes. Recent studies favored a whole blood assay to investigate the effect of anesthetics on neutrophil function [9, 10]. However, the effect of propofol or other sedative agents on the interaction between different blood cells of the human immune system has not been investigated. Since binding of activated platelets to leukocytes plays an important role in the regulation of neutrophil and monocyte function as well as in the pathogenesis of inflammatory diseases such as sepsis, we investigated whether propofol alters adhesion of activated platelets to leukocytes to gain further insight into the mechanism of anesthetic-induced immunomodulation. Using activation-dependent monoclonal antibodies and flow cytometry, we studied the effect of propofol as well as its solvent Intralipid on platelet–leukocyte adhesion, expression of platelet adhesion membrane receptors, and binding of fibrinogen to platelets in vitro.

Materials and methods

After approval of the local institutional ethics committees and the obtaining of informed consent, venous blood samples were taken from 16 healthy volunteers who had not ingested nonsteroidal antirheumatics for at least 2 weeks prior to donation. Blood was drawn via a 21-gauge butterfly cannula without tourniquet from an antecubital vein into blood collection tubes (Sarstedt, Nümbrecht, Germany) to a final concentration of 0.32% sodium citrate. The first 2 ml of blood were discarded. Blood samples of each donor were immediately diluted 1:1 with 37 °C prewarmed Dulbecco's phosphate-buffered saline (PBS without Ca^{2+} and Mg^{2+}; Sigma Chemicals, St. Louis, Mo.), which contained the desired concentration of either propofol or Intralipid. The concentration of propofol tested was that providing clinical anesthesia (4 µg/ml) and ten times this concentration (40 µg/ml) [11]. The appropriate volume of Intralipid 10% equal to the concentration of propofol being investigated was also tested, because parenteral lipid solutions are reported to influence leukocyte function. One blood sample was diluted only with PBS to serve as control. Subsequently, the blood samples were incubated for 60 min at 37 °C in a water bath. After incubation, blood samples were immediately processed for stimulation procedures and flow cytometric analysis.

Whole blood stimulation and flow cytometric analysis were performed as previously described [12, 13]. In brief, adenosine-5-diphosphate (ADP; Sigma Chemicals, St. Louis, Mo.) was used at a final concentration of 2.5 µM. After 5 min stimulation at room temperature, 100 µl of the blood samples were added to polypropylene tubes containing saturating concentrations of fluo-

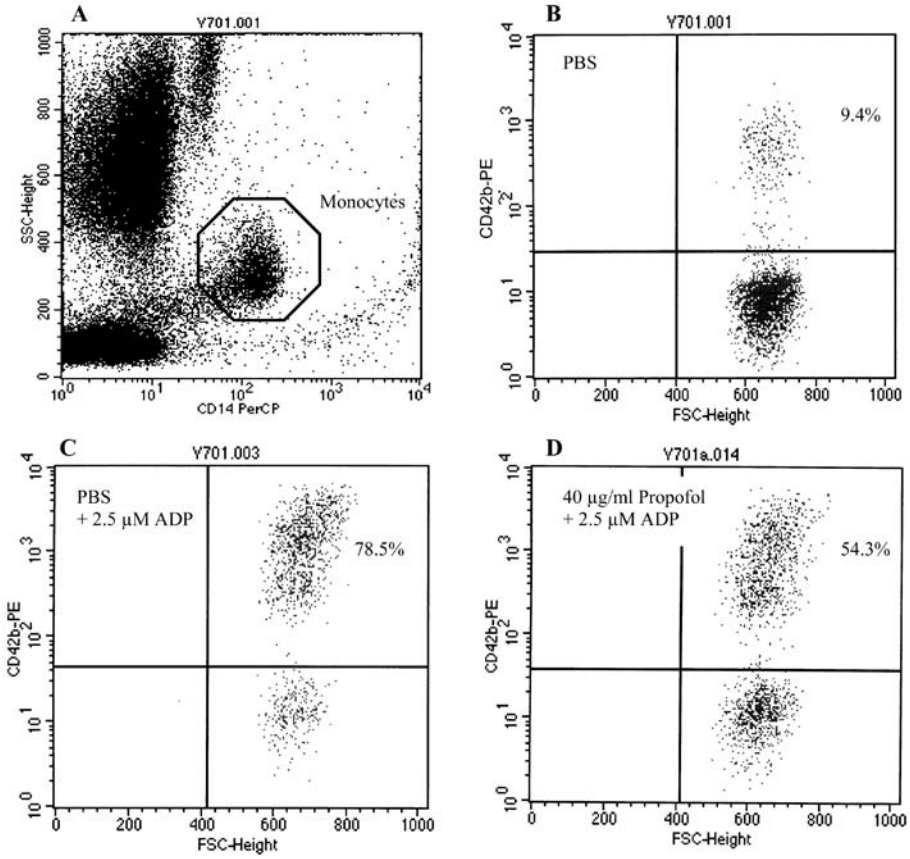

Fig. 2A–D Adjustment of the aquisition dot plots for analysis of the percentage of monocytes with bound platelets. Monocytes were identified in the sideward scatter (SSC) versus CD14-PerCP signal as acquired on the flow cytometer (**A**). The events above the horizontal line in the right upper quadrant (**B**) were considered to represent monocyte–platelet conjugates and those below the line were considered to be platelet-free monocytes, as determined by isotype control. **C** and **D** show a representative result of the inhibiting effect of 40 µg/ml propofol on the binding of ADP-activated platelets to monocytes in comparison with PBS control

rochrome-conjugated antibodies. The staining procedure was stopped after 15 min with 2 ml red cell lysing solution (Lysing Solution; Becton-Dickinson). After centrifugation (5 min, 350×g, 4°C), the samples were washed with 2 ml PBS containing 1% bovine serum albumin (BSA), centrifugated, and the remaining pellet resuspended in 500 µl PBS containing 1% BSA and 1% paraformaldehyde. The cells were stored for up to 30 min at 4 °C in the dark until flow cytometric measurements were performed.

The following antibodies (Mab) were used to measure platelet–leukocyte adhesion and expression of specific platelet surface glycoproteins: anti-CD45-FITC (clone HI30) Mab for leukocyte common antigen; anti-CD14-PerCP (clone MφP9, Becton-Dickinson) Mab recognizing a human monocyte antigen; anti-CD42b-PE (clone HIP1) Mab recognizing the α-subunit of the GPIb complex; anti-CD62P-FITC (clone AK-4) Mab directed against P-selectin expressed on platelet surface; and negative IgG_1-FITC and IgG_1-PE antibodies (clone MOPC-21) for nonspecific binding (all from Pharmingen, San Jose, Calif.). A FITC-conjugated IgG fraction of rabbit anti-human-fibrinogen (DAKO) was used as a nonspecific isotype control in the fibrinogen-binding assay.

Flow cytometric analysis

Flow cytometric analysis was performed on a FACSCalibur flow cytometer and analyzed using CellQuest 3.1 software (Becton-Dickinson, San Jose, Calif.). The cytometer was calibrated daily with fluorescence microbeads (Calibrite Beads, Becton-Dickinson).

Leukocytes were identified and differentiated into subgroups by their cell size and granularity in the forward and side scatter (SSC), as well as by their anti-CD45-FITC fluorescence (FL 1). As previously described [5, 12, 13], the histogram generated by the anti-CD45-FITC fluorescence versus SSCserved to identify neutrophils (Fig. 1), because this panleukocyte antigen is not present on erythroid cells, platelets, or platelet aggregates. Furthermore, monocytes were also identified with an anti-CD14-PerCP Mab (Fig. 2). Platelet adhesion to leukocytes was defined as neutrophils or monocytes positive for anti-CD42b-PE (FL2). The percentage of neutrophils and monocytes with bound platelets was measured (Figs. 1, 2). For each sample, 40 000 leukocytes were measured.

To determine GPIb and P-selectin expression as well as fibrinogen binding on the surface of platelets, individual platelets were identified by size (forward scatter) and anti-CD42b-PE immunofluorescence in a logarithmic scaled dot plot. Results are expressed as percentage of platelets positive for P-selectin and fibrinogen, and the mean fluorescence intensity (MFI). The anti-CD42b MFI and anti-CD62P MFI reflect the number of GPIb and P-selectin epitopes expressed on the platelet surface membrane, and the anti-fibrinogen MFI the amount of fibrinogen bound to the GPIIb/IIIa receptor per individual platelet. For each sample, 10 000 platelets were collected.

Statistical analysis

The Kolmogorov-Smirnov test showed that the flow cytometric data were not normally distributed. Thus, results are expressed as median (25th–75th percentile) unless otherwise indicated. Differences between control, Intralipid, and propofol samples were tested using the Friedman test followed by post hoc analysis (Wilcoxon test) with Bonferroni correction. A P value below 0.05 from the post hoc analysis using the Wilcoxon test was regarded as significant.

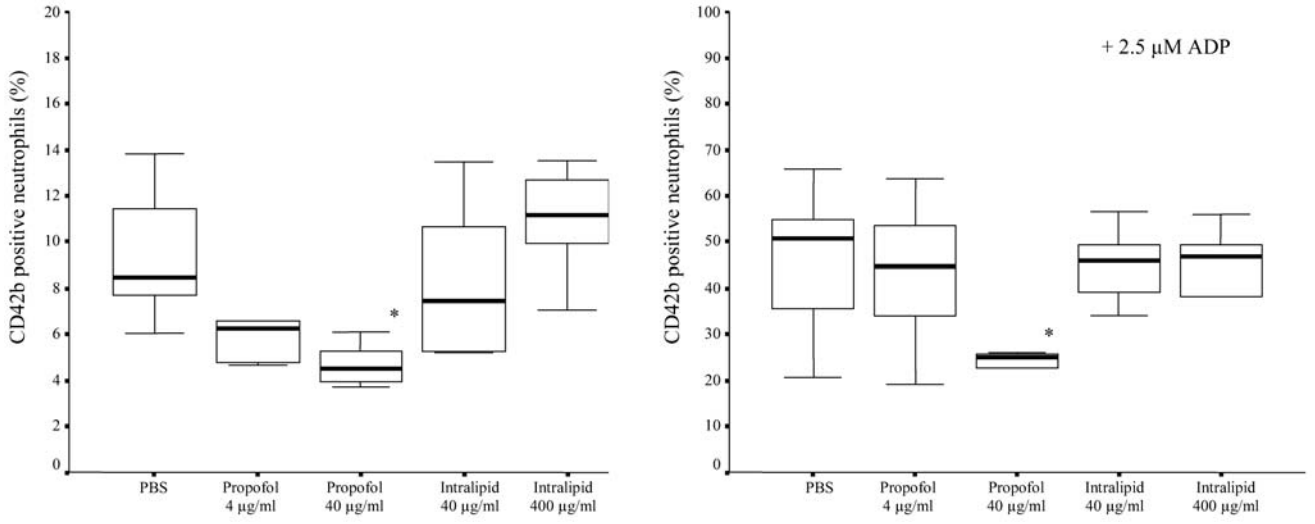

Fig. 3 Spontaneous and ADP-induced neutrophil–leukocyte adhesion following incubation with either 4 or 40 µg/ml propofol in comparison with PBS and the corresponding volume of Intralipid. *Box plots* show 25th and 75th percentiles, median, and range of eight independent experiments for each concentration of propofol and Intralipid. Values are presented as percentage of monocytes with bound platelets (% CD42b positive neutrophils). * $P<0.05$ versus PBS and 400 µg/ml Intralipid

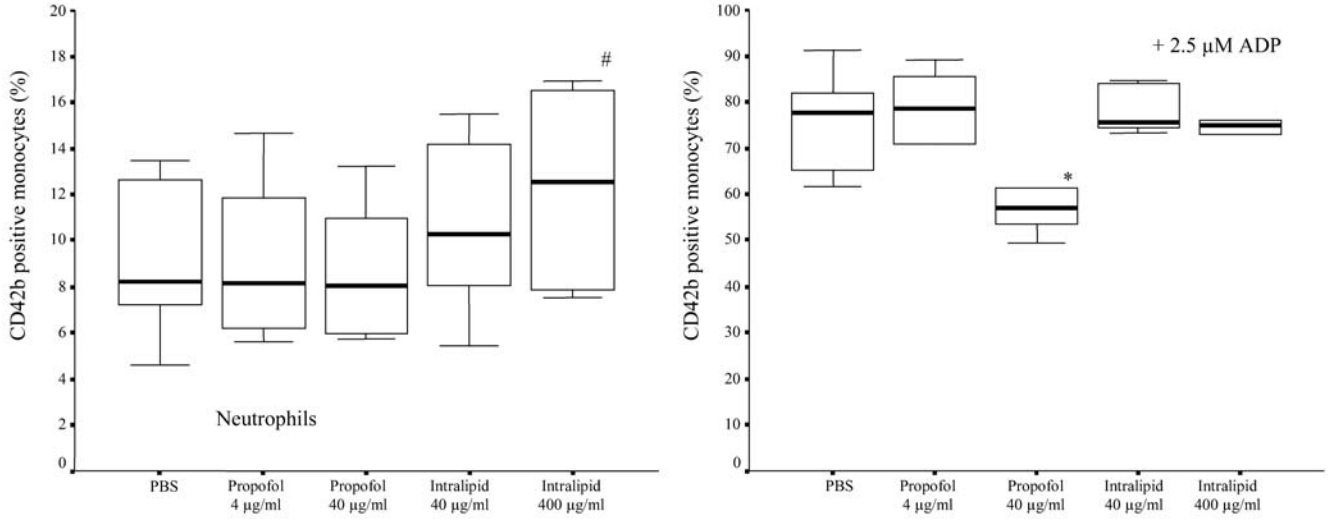

Fig. 4 Spontaneous and ADP-induced monocyte–leukocyte adhesion following incubation with either 4 or 40 µg/ml propofol in comparison with PBS and the corresponding volume of Intralipid. *Box plots* show 25th and 75th percentiles, median, and range of eight independent experiments for each concentration of propofol and Intralipid. Values are presented as percentage of monocytes with bound platelets (% CD42b positive monocytes). * $P<0.05$ versus PBS control and 400 µg/ml Intralipid; # $P<0.05$ versus PBS and 40 µg/ml propofol

Results

At the sedating concentration of 4 µg/ml, propofol did not influence the basal or ADP-induced formation of leukocyte-platelet conjugates (Figs. 3, 4), GPIb and P-selectin expression on the platelet surface membrane, and fibrinogen binding to platelets (Tables 1, 2).

After increasing the propofol concentration to 40 µg/ml we observed a significant reduction in the percentage of neutrophils with bound platelets in the unstimulated blood samples, and of neutrophils and monocytes in ADP-stimulated blood samples in comparison with PBS control and the equivalent volume of Intralipid 10% (Figs. 3, 4).

The effect of 40 µg/ml propofol on the expression of GPIb and P-selectin on the platelet surface membrane, and fibrinogen binding to platelets are shown in Table 2. After incubation with 40 µg/ml propofol, binding of fibrinogen to GPIIb/IIIa was significantly reduced compared with PBS control and the equivalent volume of Intralipid 10%. After stimulation with ADP, we observed a reduction in the percentage of platelets with bound

Table 1 Spontaneous and ADP-induced expression of P-selectin, GPIb, and fibrinogen binding to individual platelets after incubation with 4 μg/ml propofol in comparison with PBS and the corresponding volume of Intralipid. Results of eight independent experiments [median (25th–75th percentile)]. Values are presented as percentage of platelets positive for fibrinogen. The mean fluorescence intensity (MFI) in arbitrary units of FITC-anti-fibrinogen on each platelet represents the amount of fibrinogen bound to a single platelet

	PBS control	Propofol 4 μg/ml	Intralipid 40 μg/ml
P-selectin expression			
% Positive platelets	2.4 (1.4–4.6)	3.0 (2.5–6.1)	2.8 (2.0–5.7)
MFI P-selectin	17.3 (12.2–20.8)	15.7 (11.6–27–6)	22.9 (12.8–28.5)
% Positive platelets (2.5 μM ADP)	13.2 (9.1–17.7) 30.2	11.7 (7.4–23.4)	10.0 (6.4–16.2)
MFI P-selectin (2.5 μM ADP)	(24.4–35.1)	29.4 (25.0–31.0)	27.0 (19.2–33.4)
Fibrinogen binding			
% Positive platelets	7.8 (4.7–10.2)	9.1 (6.5–10.2)	10.9 (5.0–12.9)
MFI Fibrinogen	934 (615–2258)	670 (512–1501)	1004 (696–2946)
% Positive platelets (2.5 μM ADP)	72.8 (69.2–84.0)	75.0 (66.4–82.8)	74.4 (71.8–80.1)
MFI Fibrinogen (2.5 μM ADP)	1621 (1240–2071)	1550 (971–1914)	1907 (1527–2561)
MFI CD42b			
GPIb expression	946 (496–1143)	1030 (485–1250)	987 (499–1163)
MFI CD42b (2.5 μM ADP)	796 (465–1195)	822 (458–999)	805 (475–1110)

Table 2 Spontaneous and ADP-induced expression of P-selectin, GPIb, and fibrinogen binding to individual platelets after incubation with 40 μg/ml propofol in comparison with PBS and the corresponding volume of Intralipid. Results of eight independent experiments [median (25th–75th percentile)]. Values are presented as percentage of platelets positive for fibrinogen. The mean fluorescence intensity (MFI) in arbitrary units of FITC-anti-fibrinogen on each platelet represents the amount of fibrinogen bound to a single platelet

	PBS control	Propofol 40 μg/ml	Intralipid 400 μg/ml
P-selectin expression			
% Positive platelets	2.4 (1.4–4.6)	3.0 (2.0–5.8)	2.0 (1.8–5.1)
MFI P-selectin	17.3 (12.2–20.8)	13.2 (12.1–44.7)	13.4 (11.1–52.9)
% Positive platelets (2.5 μM ADP)	13.2 (9.1–17.7)	12.9 (8.1–18.9)	11.0 (8.2–19.5)
MFI P-selectin (2.5 μM ADP)	30.2 (24.4–35.1)	33.0 (26.9–45.4)	30.9 (23.4–36.9)
Fibrinogen binding			
% Positive platelets	7.8 (4.7–10.2)	6.3 (4.5–8.9)	11.7 (8.6–17.9)
MFI Fibrinogen	934 (615–2258)	249 (116–867)*	955 (518–2262)
% Positive platelets (2.5 μM ADP)	72.8 (69.2–84.0)	57.4 (53.6–65.3)*	73.4 (63.1–80.6)
MFI Fibrinogen (2.5 μM ADP)	1621 (1240–2071)	524 (454–584)*	1627 (817–2037)
GPIb expression			
MFI CD42b	946 (496–1143)	1061 (510–1276)	1001 (508–1165)
MFI CD42b (2.5 μM ADP)	796 (465–1195)	880 (783–986)	872 (799–1003)

*$P<0.05$ versus PBS control and Intralipid; #$P<0.05$ versus PBS control and propofol

fibrinogen as well as the amount of fibrinogen per individual platelet incubated with 40 μg/ml propofol.

Effects attributable to the propofol carrier Intralipid 10% were seen only at the higher concentration, which is equivalent to the amount of lipid present at the concentration of 40 μg/ml propofol (Fig. 4). Effects dependent on Intralipid were an enhanced adhesion of unstimulated platelets to monocytes, whereas platelet glycoprotein expression and fibrinogen-binding to GPIIb/IIIa was not affected (Tables 1, 2).

Discussion

Adhesion of platelets to neutrophils and monocytes represents an important event in physiological and pathological inflammation, as demonstrated in vitro [14, 15, 16] and observed in vivo [4, 5, 6, 7]. Propofol is known to affect several aspects of leukocyte [8] and platelet function [17]. However, most studies investigating the effects of propofol on neutrophil or monocyte function used isolated cells, eliminating the impact of platelets on the immunological function of these cells. Therefore, we were interested to evaluate the effect of propofol on platelet–leukocyte adhesion.

The major findings of the present study are: (1) at the clinically important concentration of 4 μg/ml, propofol does not alter adhesion of activated platelets to leukocytes. (2) The ten-fold propofol concentration inhibits the percentage of neutrophils and monocytes with bound platelets after stimulation with ADP. (3) Fibrinogen-binding to platelets is suppressed at 40 μg/ml propofol. (4) In the 40 μg/ml propofol group, expression of GPIb, which might also be a counterreceptor for neutrophil CD11b, is increased.

Propofol is known to inhibit neutrophil chemotaxis [18, 19], phagocytosis [20], respiratory burst activity [21], and IL-8 release [22]. In monocytes, propofol augmented the endotoxin-induced release of TNF-α and inhibited the release of IL-1ra [10]. However, these studies used isolated neutrophils, despite the study of Larsen et al. [10], eliminating the influence of other blood cells and intercellular mechanisms present in whole blood. Recent investigations revealed that activated platelets binding to neutrophil CD11b modulate respiratory burst activity [23] and recruitment of neutrophils to sites of inflammation [15]. Furthermore, interaction of platelets with neutrophils and monocytes enhances the ability of other mediators to induce the release of IL-1β, IL-8, and monocyte chemotactic protein (MCP-1) [14, 24]. The results of the present study demonstrated that propofol inhibits binding of activated platelets to neutrophils and monocytes in human whole blood only at concentrations that exceed the clinical relevant concentration ten times. Accordingly, we conclude that in clinically used concentrations propofol does not influence neutrophil and monocyte immune function by modifying the mutual cellular interaction between platelets and leukocytes.

Binding of platelets to leukocytes is supposed to occur in several sequential steps. First, binding of activated platelets to leukocytes is initiated by an adhesion cascade in which P-selectin binds to PSGL-1[2]. Engagement of P-selectin with PSGL-1 triggers tyrosine kinase-dependent mechanisms that lead to CD11b activation, enabling subsequent tight adhesion to platelets [25]. The CD11b counterreceptor on the platelet surface has not been definitely characterized. Two proposed receptors are fibrinogen bound to platelet GPIIb/IIIa [26, 27] and the platelet glycoprotein GPIb [28]. However, data on the role of GPIIb/IIIa as a CD11b counterreceptor are controversial. Kirchhofer et al. demonstrated complete inhibition of binding of activated platelets to leukocytes using a P-selectin blocking antibody in combination with a GPIIb/IIIa antagonist, but only partial inhibition when using the P-selectin antibody alone [15]. Weber and Springer showed that binding of activated platelets was partially blocked by an antibody against GPIIb/IIIa [26]. In contrast, results of Ostrovsky et al. did not support the role of GPIIb/IIIa-fibrinogen as the counterreceptor of CD11b [29]. Therefore, the existence of another CD11b receptor on the platelet surface has been proposed, which might be the constitutively expressed platelet glycoprotein GPIb. Since propofol inhibited the formation of platelet–leukocyte conjugates, we tried to clarify the underlying effect by measuring platelet P-selectin and GPIb expression as well as fibrinogen-binding. Propofol had no effect on P-selectin and GPIb expression. However, 40 μg/ml propofol inhibited fibrinogen binding to platelets and the percentage of platelets with bound fibrinogen following activation with ADP. Since adhesion of activated platelets to leukocytes might depend in part on the interaction of leukocyte CD11b with fibrinogen bound to platelet GPIIb/IIIa, this finding may provide an explanation for the inhibiting effect of propofol on the formation of platelet–leukocyte conjugates. However, our data do not rule out the possibility of additional effects of propofol on P-selectin-triggered mechanisms via PSGL-1 leading to activation of CD11b-dependent adhesion events.

Propofol inhibits platelet aggregation, probably by inhibiting the transient rise in intracellular calcium [17]. Furthermore, propofol is assumed to interact with G-protein, phospholipase C, protein kinase C, and mitogen-activated protein kinase p42 [30, 31]. It is possible that the inhibitory effect of propofol on platelet–leukocyte adhesion may also be mediated by interacting with these proteins and enzymes, which are involved in platelet and leukocyte signal transduction and function.

Heine et al. reported an inhibitory effect of the solvent of propofol (Intralipid 10%) on the neutrophil respiratory burst activity [21, 32]. To differentiate between the specific effect of propofol and its solvent, we compared propofol-diluted blood samples with PBS-diluted and Intralipid-diluted blood samples. Therefore, our results show that the described propofol effects are independent of its solvent Intralipid. A specific lipid effect, enhanced adhesion of unstimulated platelets to monocytes, was only seen in the 400 μg/ml Intralipid group.

In conclusion, at the concentrations in clinical use propofol does not alter the adhesion of platelets to leukocytes in vitro. Accordingly, we suggest that the propofol concentrations achieved during sedation of critically ill patients may not inhibit leukocyte immune function by modifying the mutual cellular interaction between platelets and leukocytes. Only at supraphysiological concentrations did propofol reduce the formation of platelet–neutrophil and platelet–monocyte conjugates, which is due to an inhibition of fibrinogen binding to platelets by propofol. However, since in vitro conditions do not reproduce in vivo conditions identically, additional clinical studies in critically ill patients should be continued.

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