

## PAIN ON INJECTION OF PROPOFOL: EFFECTS OF CONCENTRATION AND DILUENT

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### SUMMARY

*The emulsion formulation of propofol (Diprivan) evokes pain on i.v. injection, although its pH and osmolality are close to those of blood. The pain induced by serial dilutions of propofol in Intralipid and 5% glucose was examined in isolated vein segments and after intracutaneous injection. Propofol evoked pain in a concentration-related manner in six of eight subjects after i.v. perfusion and in all eight subjects after intracutaneous injections. Pain was maximal with propofol  $56 \times 10^{-3}$  mol litre<sup>-1</sup> when visual analogue pain scale was 60% of maximum (range 20-92%) for venous perfusion and 89% (range 66-100%) for intracutaneous injection. Dilution with 10% Intralipid reduced pain more than that with 5% glucose. We conclude that the intensity of pain after i.v. injection of propofol was related to its free aqueous concentration.*

### KEY WORDS

*Anaesthetics, intravenous: propofol. Complications: pain on injection.*

Many anaesthetic induction agents, sedatives and neuromuscular blocking drugs are formulated at a non-physiological osmolality or pH ( $> 3$  osmol kg<sup>-1</sup>, pH  $< 4$  or  $> 11$ ), which may be associated with pain on injection [1]. However, propofol evokes pain in 10-100% of patients [2-5], although the solution (Diprivan, ICI) has almost normal osmolality and pH (0.303 osmol kg<sup>-1</sup>, pH 8.0). This suggests that the substance itself is responsible for the pain evoked. To test this hypothesis, we have examined the relationship between pain intensity and concentration by perfusing serial dilutions of propofol through a vascularly isolated segment of a dorsal

hand vein and by intracutaneous injections into the forearm.

Because the free concentration in the aqueous phase of highly lipophilic agents such as propofol depends on the proportion of lipid in the emulsion, we studied the effects of propofol as dilutions of Diprivan with 5% glucose and with 10% Intralipid.

### SUBJECTS AND METHODS

Eight healthy subjects (physicians and medical students) volunteered and consented to the study, which was approved by the Committee on Medical Ethics of the University of Düsseldorf. Experiments started at 09:00 with the subjects sitting comfortably semirecumbent at a thermoneutral room temperature of 24 °C. A vein segment devoid of side branches between two valves was identified on the dorsum of the non-dominant hand. Two 14-gauge Teflon cannulae (Venflon, Viggo) were inserted from down- and upstream puncture sites. The vein segment was isolated from the systemic circulation by external air pad occluders in order to avoid systemic effects of propofol and expose the vein wall to known drug concentrations.

The completeness of the isolation of the vein segment was ascertained by absence of visible blood in the effluent and by the similarity between inflow (delivered by a calibrated precision pump) and outflow (sampled continuously in a calibrated cylinder and measured every 1 min). Two experiments were terminated because of discrepancies

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TABLE 1. Time course (s) (median (range)) of pain after intracutaneous injections and i.v. perfusions of propofol at varying concentrations with 5% glucose or Intralipid as diluent

Propofol concn (mol litre <sup>-1</sup> )	I.v. perfusions (n = 6)				Intracutaneous injections (n = 8)			
	Intralipid		5% Glucose		Intralipid		5% Glucose	
	Latency	Time to recovery	Latency	Time to recovery	Latency	Duration	Latency	Duration
0.0 × 10 <sup>-3</sup>	—	—	—	—	—	—	—	—
3.5 × 10 <sup>-3</sup>	—	—	188 (86–305)	64 (45–90)	—	—	25 (6–36)	18 (11–25)
7.0 × 10 <sup>-3</sup>	—	—	79 (12–182)	82 (31–126)	23 (7–35)	30 (16–48)	17 (8–23)	44 (11–67)
14.0 × 10 <sup>-3</sup>	319 (205–455)	20 (18–22)	61 (27–192)	133 (47–255)	24 (8–31)	65 (15–117)	11 (4–19)	61 (14–135)
28.0 × 10 <sup>-3</sup>	165 (25–335)	61 (15–146)	31 (9–71)	170 (88–233)	9 (5–17)	81 (21–145)	8 (3–15)	97 (22–171)
56.0 × 10 <sup>-3</sup>	24 (11–55)	159 (42–267)	17 (9–46)	151 (61–283)	6 (3–9)	127 (27–198)	6 (2–8)	135 (35–220)

between in- and outflowing volumes; these were followed by transitory systemic effects of propofol (slight vertigo and impaired visual acuity).

The subjects rated their pain intensity on a visual analogue scale with the help of apparatus of our own design. A handle could be moved over a distance of 80 mm to the right. A linear potentiometer gave a voltage proportional to the rated pain intensity between 0 (no pain) and 100% (maximum tolerable pain) which was recorded continuously on a Gould TA 500 Polygraph. The subjects were asked to describe the pain quality immediately after each drug concentration.

Propofol (Diprivan: propofol 56 × 10<sup>-3</sup> mol litre<sup>-1</sup> in 10% Intralipid) was diluted with either 5% glucose (oil:propofol ratio constant 10:1) or 10% Intralipid (oil:propofol ratio doubled with each degree of dilution) to yield propofol concentrations of 56, 28, 14, 7, 3.5, and 0.0 × 10<sup>-3</sup> mol litre<sup>-1</sup> (pure diluents) and perfused at 35 °C (the temperature of blood in superficial hand veins).

Each subject was studied twice on different days separated by 1–3 weeks. On one day, propofol was used with 5% glucose; on the other, 10% Intralipid was diluent. To avoid long-term alteration of the sensory structures of the vein wall, the same vein segment was not used twice.

#### Constant i.v. perfusion

After blood was washed out with saline, solutions with different propofol concentrations were perfused constantly (1.5 ml min<sup>-1</sup>) through the isolated vein segment for 10 min and there-

after rinsed with isotonic saline for 5 min. The various concentrations were studied in randomized sequence. The subjects were not informed about the propofol concentration or about the onset or termination of perfusion and rinsing periods.

#### Intracutaneous injections

Propofol (0.1 ml of different concentrations) was injected intracutaneously via a 28-gauge steel cannula into marked areas of the hairless skin of the forearm; the propofol concentrations were administered randomly and the subject did not know the actual concentration used. Skin sensation in the marked areas was tested by pinprick, touch, heat and cold at 5, 10 and 20 min after injection.

#### Data analysis

The time course in pain intensity was evaluated in terms of latency and duration of pain after intracutaneous injections and of latency and time to recovery during rinsing in the i.v. perfusion experiments.

Concentration–pain intensity relations were plotted for each subject by relating the propofol concentrations to the maximal pain for both the injection and perfusion experiments.

Differences in maximal pain for the two dilutions were tested for significance by analysis of variance (repeated measurement ANOVA) followed by Wilcoxon's test; significance was accepted at  $P < 0.05$ .

## RESULTS

Propofol evoked pain in a concentration-related manner in six of eight subjects during perfusion of isolated vein segments and in all eight subjects after intracutaneous injections.

Regardless of the site of application, pain occurred earlier and lasted longer with increasing concentrations of propofol (table I).

There was considerable interindividual variability in the time course of pain. With i.v. perfusion, latency was 9–55 s and time to recovery

42–283 s after application of pure Diprivan. For both i.v. and intracutaneous application, pain intensities increased with the concentration of propofol and, at a given concentration, were always greater with glucose than with Intralipid as diluent (fig. 1). After i.v. application (data from six subjects who experienced pain during perfusion), pain occurred with propofol  $3.5 \times 10^{-3}$  mol litre<sup>-1</sup> (5% of the visual analogue scale on the average) with glucose but with propofol  $14 \times 10^{-3}$  mol litre<sup>-1</sup> (4% of the visual analogue scale on the average) when Intralipid was diluent. With both diluents, pain intensities increased with the concentration of propofol, to a mean maximum of 60% (range 20–92%) of the visual analogue scale at  $56 \times 10^{-3}$  mol litre<sup>-1</sup> (undiluted Diprivan).

Similar results were obtained with intracutaneous injections, which evoked pain in all eight subjects. Pain occurred with propofol  $3.5 \times 10^{-3}$  mol litre<sup>-1</sup> (6% of the visual analogue scale) in glucose and with propofol  $7.0 \times 10^{-3}$  mol litre<sup>-1</sup> (1% of the visual analogue scale) with Intralipid as diluent. With increasing concentration of propofol, pain increased also, but to a greater degree than during i.v. perfusion; it reached a maximum of 89% (range 66–100%) of the visual analogue scale with undiluted Diprivan.

Regardless of the site of application, dilutions of Diprivan with Intralipid evoked significantly less pain than those with 5% glucose. It should be noted that the diluents never elicited pain. After intracutaneous injections, all subjects noted changes in skin sensitivity over the site of injection which developed within 5 min. They experienced pinprick and warm stimuli as more intense in the presence than in the absence of propofol, although they did not feel cold and touch sensations. These effects occurred only with painful concentrations of propofol, but never with Intralipid or glucose alone. Skin sensitivity returned to normal in all subjects within 20 min. The evoked pain was described as burning and oppressive during i.v. perfusion and mainly as burning after intracutaneous injection.

All subjects suffered from minor venous sequelae such as hypersensitivity to touch and perivascular oedema and flush for several hours. In five of eight subjects, the vein segments became indurated for up to 3 weeks, but thereafter regained normal appearance and function.

After intracutaneous injection of the drug, a

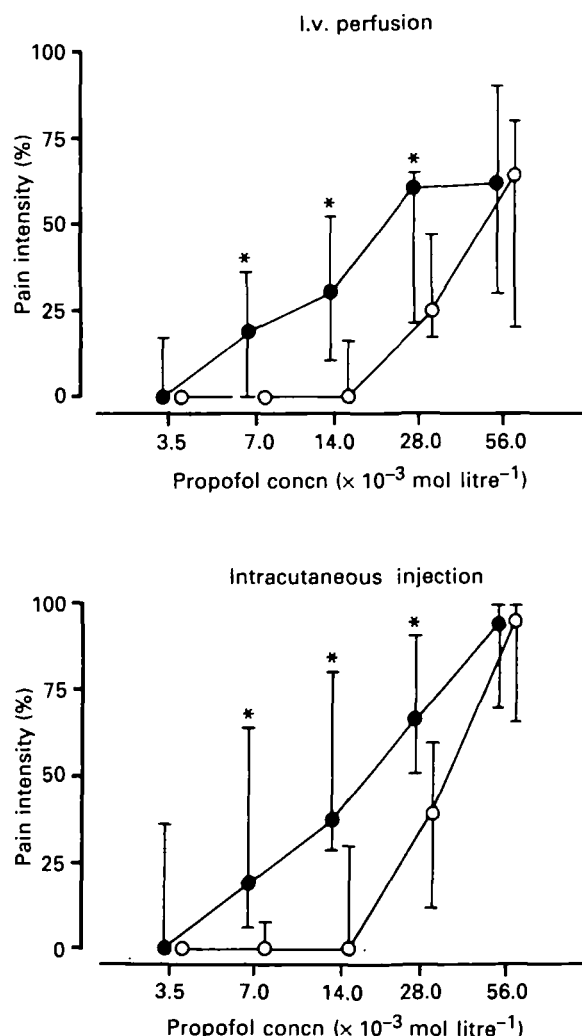


FIG. 1. Effect of propofol concentration on maximum pain (medians and ranges) measured on a visual analogue scale during i.v. perfusion ( $n = 6$ ) and intracutaneous injection ( $n = 8$ ).  $\circ$  = dilution of Diprivan with Intralipid;  $\bullet$  = dilution of Diprivan with 5% glucose. \*  $P < 0.05$ .

rapid flush developed round the site of application, but no long term sequelae occurred.

#### DISCUSSION

The results of this study suggest that the pain induced by i.v. and intracutaneous administration of propofol is a function of the drug itself rather than the formulation. The pain induced was related to the aqueous concentration of propofol, as shown by the lesser degree of pain induced by dilutions of Diprivan with Intralipid compared with those with 5% glucose.

The isolated vein technique for investigating the mechanisms of induction of pain on i.v. injection of drugs has several advantages. The i.v. concentration of propofol could be maintained constant in the absence of protein binding, dilution and buffering by blood. The exposure time of 10 min should have been sufficiently long for a highly lipophilic agent such as propofol to establish a concentration equilibrium across the intima to the venous nociceptors [6].

Propofol evoked pain in six of eight subjects during i.v. perfusion, but with latencies of up to 55 s—that is, over time periods when patients have usually lost consciousness after i.v. injection. This is in accord with the increase in incidence and intensity of pain after slow injection of propofol [7].

Dilution of Diprivan with Intralipid may be a useful addition to other means advocated for reducing pain on injection, such as the use of a large diameter vein [7], prior administration of aspirin or opioids [8, 9], addition of local anaesthetic drugs [7, 9–12] or cooling [13].

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