Intraarterial Propofol Is Not Directly Toxic to Vascular Endothelium


To determine if accidental intraarterial injection of propofol results in vascular damage, the effect of bolus administration of propofol on vascular smooth muscle and the endothelium was investigated using the isolated rabbit ear artery. Ear artery segments, removed from urethane anesthetized rabbits, were perfused with Krebs solution (1 ml min⁻¹) and pressurized to 60 mmHg before being constricted with extraluminal norepinephrine (1.8–4.2 × 10⁻⁶ M). The external diameter of the vessel was measured by an array of light-dependent diodes. Functional responsiveness was determined by the degree of constriction to norepinephrine and the subsequent dilatation of the artery to intraluminal acetylcholine (2 × 10⁻⁶ M) and glyceryl trinitrate (2 × 10⁻⁶ M), and by the myogenic reactivity to a pressure increase from 60 to 100 mmHg. These responses were measured before and after perfusion with 1% propofol for 120 s. Administration of propofol did not result in any vasoactivity nor did it increase the sensitivity to norepinephrine. Vessels maintained their capacity to dilate to both agents, while the myogenic activity was unaffected. Histologic examination of the propofol exposed vessels showed no changes to smooth muscle structure, and the endothelial layer remained intact. (Key words: Anesthetics, intravenous; propofol. Complications: intraarterial. Muscle, smooth; artery. Endothelium: endothelium-derived relaxing factor.)

Although relatively uncommon,¹,² the inadvertent intraarterial injection of anesthetic drugs can result in local ischemia and eventual tissue necrosis. There are data detailing the sequelae of intraarterial administration of induction agents such as thiopental,³,⁴ but there is little information on the intraarterial effects of the more recently introduced agent⁵,⁶ diisopropyl phenol (propofol). Although recent case reports of intraarterial injection of propofol suggest that serious complications are unlikely,⁵−⁷ there have been no laboratory studies to assess whether bolus injection of propofol results in any direct alteration to the structure or function of the artery. The experiments explained here were designed to investigate arterial responses during and after intraarterial administration of propofol.

Materials and Methods

Vessel Preparation

Experiments were carried out with the approval of the University of Tasmania’s Animal Ethics Committee. New Zealand semi–lop–eared rabbits (1.75–3.23 kg) of either sex and between 8–12 months were anesthetized with intravenous urethane (1.7 g kg⁻¹), and the proximal 2–3 cm segment of the central ear artery was removed, to avoid unnecessary contact with the vessel during dissection. Vessels were used either immediately or, in some instances, within 12 h of their removal, after they had been stored at 2°C in a Krebs solution of the following millimolar composition: NaCl 118, KCl 4.69, NaHCO₃ 25, KH₂PO₄ 1.08, CaCl₂ 2.52, MgSO₄ · 7H₂O 1.05, and dextrose 5.55.

Perfusion Apparatus and Techniques

The apparatus used was modeled on that described by Speden and Speden and Warren,⁹ modified by the incorporation of a servomechanism-infusion pump governed by a Hewlett-Packard 3110B Function Generator capable of maintaining constant intraluminal pressure during changes in resistance or vessel diameter. Arterial segments were transferred to a 4.2-ml perfused organ bath; the proximal end was mounted and tied onto a 19-G blunted cannula and then flushed out and filled with Krebs solution before the distal end was likewise cannulated and tied. The Krebs solution, used as both the intraluminal perfusate and the organ bath exchange solution, was drawn from a common reservoir, which was bubbled with 95% O₂–5% CO₂. Intraluminal flow was set at 1 ml min⁻¹ and monitored by means of a drip counter mounted distal to the outflow resistor. The intraluminal pressure was increased to 150 mmHg to test for leaks, and the distance between the cannulae adjusted to remove any bowing, such that the final length of the artery approximated that in vivo. Any excess connective tissue was removed and the servomechanism pump adjusted to provide a pressure of 60 mmHg.

The vessel segments, which had a final length between cannulae tips of 5–8 mm, were allowed to equilibrate under these conditions for 30 min. Organ bath fluid was
replaced at the rate of 4 ml · min⁻¹ by a peristaltic pump (Watson-Marlow 202U), and the temperature was maintained within the limits of 32–33°C with circulating water, monitored by a digital thermometer (Analog Devices 2036-T-4112), using a thermocouple mounted within the bath.

The artery was illuminated from below with an Olympus LSE light source directed through a red filter. The external diameter of the vessel was calculated from the width of the shadow cast by the tissue on a linear array of self-scanning photodiodes§ (Reticon RL1024G) mounted at right angles to the long axis of the vessel. This photodiode array was scanned every 10 ms, and the resulting processed signal, representing the external diameter, was monitored on an oscilloscope (Trio CS-1040) and recorded to the nearest 5 μm on a chart recorder (Yokogawa 5066). A cover slip, placed across the bath well, was used to remove the meniscus of the bath solution.

The intraluminal perfusion pressure was recorded using a pressure transducer (Statham P23 Db) mounted between the artery segment and the variable outflow resistor.

Solutions of (−)-norepinephrine hydrochloride (Sigma) were made in 0.9% NaCl. Using a syringe pump (model 355, Sage Instruments), the norepinephrine solution was added to the extraluminal perfusate at a rate of 0.1 ml · min⁻¹ to induce a constriction of the vessel of approximately 50% of maximum. The final mean norepinephrine bath concentration was 2.85 × 10⁻⁶ M.

**Assessment of Vascular Muscle and Endothelial Cell Function**

After the equilibration period, the artery was constricted with extraluminal norepinephrine, and the vessel was subjected to three separate procedures, performed in random order, to determine myogenic reactivity and the responses to endothelium-dependent and -independent vasodilators.

First, the myogenic reactivity of the vessel was assessed from the response to pressure increases produced using the Hewlett-Packard Waveform Generator. Pressure within the vessel was increased from 60 to 100 mmHg within 500 ms and maintained at that level for 120 s, before returning to the starting pressure. Under these conditions, vessels dilate from their initial diameter (D₀) to a maximal diameter (Dₘ) before contracting against the pressure increase to a final diameter (Dₖ), before return of the pressure to 60 mmHg. Myogenic responsiveness can be assessed by determining the segment recovery, which reflects the capacity of the vessel to return to Dₖ against the pressure increase and is calculated from the ratio of ([Dₘ - Dₖ]/[Dₘ - D₁]). Previous experiments have shown recovery to be greater than 0.75.

Second, the presence of a functional endothelium and the vessel response to endothelium-derived relaxing factor (EDRF) was confirmed by rapid and sustained dilatation to acetylcholine chloride (ACh) solution (Sigma) added to the intraluminal perfusate, in a final concentration of 2 × 10⁻⁶ M.

Third, the response of the vessel to endothelium-independent vasodilation was determined from the administration of 2 × 10⁻⁶ M glyceryl trinitrate (GTN) solution (DBL Laboratories).

Dilation was measured by the increase from D₁ to Dₘ, after addition of the dilator substance. Using these data and incorporating the opening, unconstricted diameter of the pressurized vessel (Dₙ), the percentage dilatation (Pₐₙ) of vessels to both ACh and GTN was determined from the formula ([Dₘ - Dₖ]/[Dₙ - D₁]), expressing the result as a percentage. Pₐₙ represents the observed dilatation from a given D₁ as a fraction of the theoretical maximum dilatation of which the vessel is capable.

**Propofol Administration**

After 30 min, intraluminal Krebs perfusate was interrupted for 120 s by the infusion of 20 ml of propofol 1% solution through a side line mounted immediately proximal to the vessel segment. Vessel diameter was measured throughout, and care was taken not to allow air to come into contact with the luminal surface at any time. At the conclusion of the 2-min period, the Krebs perfusion was recommenced, and after an additional 5 min, the procedures detailed above were repeated. Data in the text are presented as mean ± standard error of the mean (SEM). Significance was set at P < 0.05 and determined by the paired Student’s t test.

**Results**

**Dilatation**

Vessel segments (n = 8), with a mean Dₙ of 1,361 ± 11 μm were constricted with norepinephrine (range 1.8 – 4.27 × 10⁻⁶ M). Prior to the administration of propofol, vessels dilated in response to ACh (2 × 10⁻⁶ M) from D₁ 972 ± 54 μm to Dₘ 1,285 ± 14 μm. After pro-

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§ External (rₓ) and internal (rᵢ) vessel diameters are directly proportional within limits. Assuming that the cross sectional area of the vessel wall (A) remains constant,

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rᵢ = \sqrt{rₓ² - \frac{A}{\pi}}
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pofol administration, the measurements for $D_i$ and $D_m$ were $964 \pm 36$ and $1,260 \pm 10$ respectively. In response to GTN, vessels dilated from $D_i = 1,004 \pm 33$ to $D_m = 1,283 \pm 20 \mu m$ before propofol administration and from $985 \pm 35$ to $1,250 \pm 27 \mu m$ after propofol administration. $P_{dt}$ for ACh was $79 \pm 2\%$ before and $74 \pm 3\%$ after propofol administration and for GTN was $79 \pm 5\%$ and $72 \pm 7\%$ respectively. There are no significant differences in any of these data sets.

**HISTOLOGIC EXAMINATION**

At the conclusion of each experiment, vessels were subject to histologic examination. As a separate experiment, three additional vessels were prepared as described in Materials and Methods but were not exposed to propofol to confirm that the processes of mounting, perfusion, and preservation had had no adverse effects on vascular microstructure. In each case, specimens were fixed in phosphate buffer ($pH = 7$) containing gluteraldehyde 4\%, paraformaldehyde 2\%, and cocodylate 0.1 M and postfixed in osmium tetroxide with uranyl acetate 4\% and embedded in Epon before staining with toluidine blue. Photomicrographs of 0.2 - 0.5-\mu m sections were taken, and these confirmed that in vessels exposed to propofol, the endothelial cell layer remained intact and there were no changes to smooth muscle structure (fig.1).

**MYOGENIC RESPONSE**

After a rapid pressure increase from 60 to 100 mmHg, vessels responded with an initial $D_i = 891 \pm 17 \mu m$ to a $D_m$ of $1063 \pm 10.8 \mu m$ before constricting against the pressure increase to a $D_i$ of $920 \pm 15 \mu m$. After propofol administration, these values were $D_i = 897 \pm 20$, $D_m = 1,081 \pm 9.7$, and $D_i = 917 \pm 21 \mu m$. In all cases the myogenic response was complete within 100 s. There were no significant differences in these data or in vessel recovery which were $0.84 \pm 0.036$ before and $0.88 \pm 0.042$ after propofol administration.

**RESPONSE TO PROPOFOL INFUSION**

After commencement of the propofol infusion, segments consistently demonstrated a prompt dilatation to $1,299 \pm 27 \mu m$, which was maintained for the duration of the infusion. Vessel diameter returned to pre-treatment levels within 5 min.

**NOREPINEPHRINE SENSITIVITY**

Pooled measurements of $D_i$ from the eight vessels before GTN or ACh administration or myogenic pressure increase ($n = 24$) were $955 \pm 29 \mu m$ before and $948 \pm 27 \mu m$ after propofol administration. There is no significant difference between these groups, suggesting that there is no increase in sensitivity to exogenous norepinephrine.

**Discussion**

A survey of the literature has revealed, to date, that only three cases of intraarterial administration of propofol have been reported. These involved the injection of 2-8 ml of 1\% propofol aqueous emulsion (Diprivan) into the brachial artery, which was followed by the rapid onset of severe pain radiating from the injection site to the hand. In one of these cases, an associated oval area of skin

![Fig. 1. Photomicrographs of sections of rabbit ear artery before (left) and after (right) exposure to 1\% propofol for 120 s. The layer of endothelial cells has remained intact, and there is no damage to either intima or smooth muscle.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931331/ on 05/28/2018)
blanching surrounding the injection site that later became hyperemic was reported. This was not observed in the other two cases, perhaps because of rapid flushing with normal saline in one case or the effects of lidocaine 2%, which had been mixed with the propofol before administration to reduce pain on injection in the other. Lidocaine is a known vasodilator and has been used to reduce the risk of ischemia following accidental intraarterial thiopental injection. In all three cases there was no permanent tissue damage and no need either for specific intervention or for an increase in the duration of hospitalization.

Assessment of the risk of major sequelae after intraarterial injection of drugs has, in the past, relied on the outcomes of clinical cases such as these. However, laboratory studies have been valuable in confirming such reports and investigating their pathogenesis. One of the earliest and most popular models was developed by Kinmonth and Shepherd, in which agents were administered into the rabbit central ear artery and the extent of subsequent tissue necrosis was used as a measure of intraarterial toxicity. Experiments based on this method have provided useful data in the past, but many animal ethics committees would now object to its use.

The method used in this report uses the standard rabbit ear artery as an in vitro model. Although the artery in this model has the disadvantage of being denervated and is not blood-perfused, it allows for a detailed investigation of structural and functional tissue changes, and vessel response can be studied directly both during and after drug administration.

Studies using thiopental have suggested that there are many mechanisms that might account for the picture of compromised vascular supply with consequent ischemia after intraarterial injection. These have included direct arterial constriction, release of or increased sensitivity to norepinephrine, destruction of vascular tissue, particulate embolisation, or a chemical incompatibility with blood. Recently, using similar methodology to that described here, we have shown that intraarterial thiopental results in the destruction of vascular endothelial cells with a consequent loss of EDRF release and exposure of the intima. Since EDRF is known to play an important role both as a vasodilator and as an inhibitor of platelet aggregation, this represents another possible mechanism by which intraarterial drug injection may result in vascular impairment.

The results of this investigation do not exclude the possibility that intraarterial propofol might adversely affect aspects of vascular supply by, for example, attenuating capillary blood flow by particulate embolization or by physical interaction with blood components. Indeed, these effects may be responsible for the local hypoperfusion observed in the cases reported.

We have shown that after intraarterial administration of propofol in the perfused pressurized isolated rabbit ear artery, there were no resulting statistically significant changes in vessel function. There were no significant differences in pooled Di data before and after propofol administration, implying that the vessel showed no increased sensitivity to catecholamines, nor was there any evidence of sustained endogenous release. Dilatation to both ACh or GTN was unaltered, and the myogenic response likewise showed no significant change. No vascular spasm or constriction was observed either during or after propofol administration; indeed during the injection process vessels consistently demonstrated marked dilatation. Although there have been reports of vasodilatation in isolated artery segments after propofol administration, it cannot be said with certainty that a direct smooth muscle relaxant effect is responsible in this case, because the rapid rate of injectate infusion, designed to simulate what might occur in vivo, may also have contributed.

In summary, the results of this investigation, when considered in conjunction with anecdotal clinical evidence, suggest that inadvertent intraarterial administration of propofol does not result in local constriction or damage to vessel structure and that major ischemic sequelae, at least from the mechanisms examined here, are unlikely.

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References