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Role of the Endothelium in the Relaxation Induced by Propofol and Thiopental in Isolated Arteries from Man

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Abstract

Induction of anaesthesia with intravenous propofol and thiopental is often accompanied by hypotension. This study evaluates whether propofol and thiopental induce relaxation of isolated arteries from man and whether this effect is modulated by the endothelium.

Mesenteric artery rings (with and without endothelium) from 12 patients were placed in organ baths and pre-contracted with phenylephrine before addition of propofol (10^{-3} M) or thiopental (10^{-3} M). Relaxation induced by propofol and thiopental was evaluated for rings with intact endothelium in the presence of the nitric oxide synthase inhibitor N^G-nitro-L-arginine methyl ester (L-NAME; 10^{-4} M) or the cyclooxygenase inhibitor indomethacin (10^{-5} M). The vasodilator effect of propofol was similar for intact and denuded endothelium rings whereas the relaxation induced by thiopental was significantly attenuated in denuded-rings. In intact endothelium rings, L-NAME and indomethacin caused marked inhibition of the relaxation induced by thiopental, but not that induced by propofol.

These results suggest that propofol induces endothelium-independent relaxation of isolated mesenteric arteries in man, whereas thiopental causes endothelium-dependent relaxation mediated by nitric oxide and prostaglandins.

Propofol (2,6-diisopropylphenol) has been proven to be a useful alternative to thiopental as an induction agent in clinical anaesthesia, although the use of both agents is often accompanied by hypotension. Several in-vivo studies of animals and man suggest that propofol reduces peripheral vascular resistance (Rouby et al 1991). In-vitro studies using excized animal vessels indicate that propofol at high concentrations dilates vessels via calcium-channel blockade (Yamanoue et al 1994). The role of endothelium-derived vasodilators has also been studied, but with conflicting results. Propofol was found to stimulate the release of nitric oxide from cultured porcine aortic endothelial cells (Petros et al 1993); in contrast, it has been suggested that propofol induced inhibition of nitric oxide production in rat aortic rings (Park et al 1992). Similarly mechanisms of action postulated for thiopental are scarce and controversial, e.g. both constrictor and relaxant effects have been reported (Terasako et al 1994; Yakushi et al 1995). This study evaluates whether propofol and thiopental induce relaxation of isolated mesenteric arteries from man and whether this effect is modulated by the endothelium.

Materials and Methods

Drugs

Propofol was a gift from Zeneca Pharmaceuticals and was dissolved in ethanol (final concentration of ethanol was less than 0·1%). Previous experiments had shown that this vehicle has no effect on arterial rings. Thiopental was purchased from Abbot Laboratories (Pentothal) and dissolved in distilled water. Indomethacin was dissolved in 5% w/v $NaHCO_3$ and N^G-nitro-L-arginine methyl ester (L-NAME) in isotonic saline; both drugs were purchased from Sigma (UK).

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Tissue preparation and isometric tension recording

The study was performed with the mesenteric arteries from man which were the most available. They were taken from portions of mesocolon during colon neoplasia surgery from 12 patients (5 men and 7 women) 56 to 76 years old. After removal of adhering tissue under a dissecting microscope, mesenteric arterial rings (4 mm long, 1–3 mm o.d.) were cut and placed in organ baths containing modified Krebs solution (in mM: $NaCl_2$ 2·5, $MgCl_26H_2O$ 1·1, $NaHCO_3$ 24, K_2EDTA 0·02, glucose 5; 5 mL) at 37°C and oxygenated with 5% CO_2 95% O_2. The mechanical activity of the rings was measured isometrically by use of a transducer (Grass FT-03) connected to a polygraph (Grass 7F) and a 1–4-g pre-load was used when the optimum tension had been determined by preliminary experiments.

Experimental protocols

After 1 h stabilization, tissue responsiveness was assessed by consistent contraction to a submaximum concentration of KCl (60 mM). After a wash-out period each ring was contracted with phenylephrine (10^{-5} M) and the relaxation induced by addition of acetylcholine (10^{-6} M) to the organ bath was used to confirm the viability of the vascular endothelium. Thereafter, mesenteric rings were pre-contracted with phenylephrine (10^{-6}–3×10^{-5} M), to induce similar increased tone in rings with and without endothelium, then propofol (10^{-3} M) or thiopental (10^{-3} M) were tested. Tissues with intact endothelium were separately incubated for 20 min with the nitric oxide inhibitor L-NAME (10^{-4} M) or the prostaglandin-synthesis

inhibitor indomethacin (10^{-5} M) before addition of propofol or thiopental.

To confirm the data obtained with this novel anaesthetic, cumulative concentration–response to propofol (10^{-5}–10^{-3} M) was measured by use of mesenteric arteries (with and without endothelium) from male Sprague Dawley rats.

Data analysis

Relaxation is expressed as the percentage reduction in the tone induced by phenylephrine (10^{-5} M). Data are shown as mean ± s.e.m. of results from n vessel rings. When appropriate, Student's *t*-test was used; more than two groups were compared by one-way analysis of variance then Scheffe's range test. All values are expressed as mean ± s.e.m. $P < 0.05$ was considered to indicate statistical significance.

Results

The contraction induced by phenylephrine in rings with intact endothelium (1838 ± 243 mg, n = 14) was not significantly different from that obtained for endothelium-denuded rings (1679 ± 334 mg, n = 11). Functional studies with acetylcholine (10^{-6} M), which induces endothelium-dependent relaxation, demonstrated that in preparations with intact endothelium acetylcholine caused significant relaxation of the contraction induced by phenylephrine (72 ± 3·7%, n = 29) but lacked any effect (4·1 ± 2·8%, n = 12) on denuded rings.

In preliminary experiments, concentration–response studies with both thiopental and propofol showed that concentrations between 10^{-6} M and 10^{-4} M induced no response by mesenteric arterial rings from man, either with (n = 5) or without (n = 3) endothelium, previously pre-contracted with phenylephrine. At a concentration of 10^{-3} M, however, both drugs produced significant ($P < 0.001$) and marked relaxation of phenylephrine-induced contraction. A 10^{-3} M concentration was, therefore, used for further studies.

Propofol (10^{-3} M) and thiopental (10^{-3} M) induced a similar level of relaxation in arterial rings, with endothelium, from man (Tables 1 and 2). In endothelium-denuded rings the relaxation induced by thiopental was significantly reduced by 37·2 ± 10·7% (n = 6). Incubation of intact rings with L-NAME and indomethacin significantly ($P < 0.01$) inhibited the relaxation induced by thiopental by 51·6 ± 11·9% (n = 5) and 60·8 ± 18% (n = 3), respectively (Table 1). In endothelium-denuded rings, the relaxation induced by propofol was not modified. L-NAME and indomethacin had no effect on the relaxation induced by propofol (Table 2).

Table 1. Relaxation induced by thiopental in isolated arteries from man.

Thiopental (10^{-3} M)	n	% Relaxation
Control with endothelium	6	80·9 ± 6·9
+ L-NAME	5	39·2 ± 9·6**
+ indomethacin	3	31·6 ± 14·6**
Control without endothelium	6	50·8 ± 8·7*

Relaxation is expressed as the percentage reduction in the tone induced by phenylephrine (10^{-5} M). Significant differences from the respective control group with endothelium are shown as *$P < 0.05$ and **$P < 0.01$.

Table 2. Relaxation induced by propofol in isolated arteries from man.

Propofol (10^{-3} M)	n	% Relaxation
Control with endothelium	8	83·1 ± 6·3
+ L-NAME	4	70·3 ± 12·2
+ indomethacin	3	85·6 ± 8·7
Control without endothelium	5	72·5 ± 9·1

Relaxation is expressed as the percentage reduction in the tone induced by phenylephrine (10^{-5} M).

Discussion

This study with isolated mesenteric artery from man clearly demonstrated the vasodilative effect of propofol and thiopental. This finding is in accord with clinical reports which show a reduction in arterial pressure after administration of propofol and thiopental, probably because of a reduction in systemic vascular resistance (Rouby et al 1991). Our results show, furthermore, that the vasorelaxation induced by propofol was endothelium-independent, whereas that induced by thiopental was endothelium-dependent and involves both nitric oxide and prostaglandins.

Although it has been suggested that clinically relevant concentrations of propofol did not have a direct vasodilator effect (Nakamura et al 1992), multiple variables affect the in-vivo environment (Bridges et al 1993) and it is, therefore, difficult to infer specific tissue drug levels. Because studies in man show that thiopental and propofol reduce vascular resistance, a concentration that dilates vessels must be used in in-vitro studies of the mechanism of vascular relaxation. Our results, and those of other workers, showed, moreover, that low concentrations of propofol (Nakamura et al 1992) and thiopental (Rich et al 1994) induce no relaxation of the vessels whereas high concentrations caused relaxation (Coughlan et al 1992; Park et al 1992).

Reports of the effect of thiopental in vessels are scarce and controversial. A study of rat aorta and pulmonary artery rings showed no relaxation response to thiopental (Park et al 1992) but another study using the same drug and the canine coronary artery demonstrated a relaxation response (Coughlan et al 1992). Our study of the mesenteric artery from man is the first to demonstrate that thiopental-induced relaxation is endothelium-dependent and is mediated by the release of nitric oxide and prostaglandins.

The endothelium-independent relaxation induced by propofol in isolated mesenteric artery from man has also been observed in porcine coronary artery rings (Yamanoue et al 1994). Studies of rat aorta and pulmonary artery rings showed endothelium-dependent relaxation, however (Park et al 1992). This endothelium-dependent relaxation in response to propofol has been associated with the release of prostaglandins and nitric oxide (Park et al 1992; Petros et al 1993). Previous studies of rat mesenteric artery in our laboratory are in agreement with these results from different rat arteries, and show differences in the concentration-dependent relaxation curve for propofol for intact or denuded endothelium rings (data not shown). The different roles reported for the endo-

thelium in propofol-induced relaxation might, therefore, be related to variability between species. Other authors, moreover, propose diverse mechanisms responsible for the vasodilator effect of propofol, e.g. antagonism of calcium channels (Yamanoue et al 1994). Our study of mesenteric arteries from man shows that the vasodilator response to propofol was not modified by indomethacin or L-NAME, which is in accord with an endothelium-independent effect.

Our findings demonstrate that thiopental, but not propofol, induces an endothelium-dependent relaxation in mesenteric arteries from man. This is in agreement with another report (Nakamura et al 1992) which suggests that both anaesthetics are unlikely to share the same site of action.

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