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Vascular effects of propofol: smooth muscle relaxation in isolated veins and arteries

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Abstract—Isolated hepatic portal veins and aorta taken from the rat were used to investigate the direct action of the intravenous anaesthetic propofol. This compound is known to produce a fall in blood pressure in man and animals and it has been suggested that the hypotension may result from a direct vasodilator action on the veins and arterioles. In our experiments propofol caused a dose related decrease of potassium-induced tone in both types of blood vessel. However, the concentrations required to produce this effect in the experiments on veins were significantly lower than those required to produce similar changes in the isolated artery preparation. We conclude that this direct action may contribute towards the hypotensive effects of propofol.

Clinical investigations have shown that induction of anaesthesia using the intravenous agent propofol (Diprivan, ICI) is associated with a decrease in blood pressure (Cummings et al 1984; Kay et al 1985; Grounds et al 1985). In an attempt to resolve the mechanism of the hypotensive activity, Goodchild & Serrao (1989) used an anaesthetised dog preparation in which all neurogenic cardiovascular reflexes had been abolished by pharmacological and surgical means. In these circumstances they were able to demonstrate that blood propofol concentrations covering the clinical range in man cause direct vasodilatation in the absence of sympathetic or vagal influences. They concluded that this direct action is responsible for the clinically observed cardiovascular effects of the anaesthetic. They were also able to show that while lower blood concentrations selectively produced venodilatation, higher concentrations were required before arteriolar dilatation became evident.

The experiments described here were undertaken in an attempt to verify these findings by examining the direct actions of propofol on isolated venous and arterial tissue from the rat.

Materials and methods

Rat isolated hepatic portal vein and aorta preparations. Small lengths of aorta and hepatic portal vein were prepared using a procedure adapted from that described by Cohen & Wiley (1978) for jugular veins. Male Wistar rats (150–250 g) were anaesthetized using halothane. A ring section of hepatic portal vein or aorta approximately 5 mm in length was removed and placed in Krebs-Henseleit solution at room temperature (20°C). At this point the rat was killed with an overdose of anaesthetic. Each ring was mounted between two L-shaped hooks bent from hypodermic needles (25 gauge). It was then secured in a 50 mL organ bath by means of ligatures which fixed one hook to the base of the bath whilst the other was attached to an isometric transducer. The tissue was bathed in Krebs-Henseleit solution, perfused with 95% oxygen and 5% carbon dioxide, and maintained at 34°C. Changes in tension of the tissue resulting from contraction or relaxation were displayed on a pen recorder (Lectromed Mx 216).

A resting tension of 1 g was applied and the preparation left to equilibrate for 1 h. Tone was induced by adding potassium chloride at a bath concentration of 40 mM. Once a constant tone had been established, doses of propofol were added every 5 min (vein) or 25 min (aorta) such that the bath concentration of drug was successively increased from 1×10^{-7} to 1×10^{-2} M. The maximum percentage reductions in the KCl-induced tone resulting from each concentration of propofol were used to construct log concentration-response curves for the two tissues. Two such curves were obtained from each of four portal veins and four aortas.

Drugs and solutions. Propofol was supplied by ICI Pharmaceuticals. The composition of the Krebs-Henseleit solution was (g L^{-1}): NaCl 6·9, KCl 0·35, $CaCl_2H_2O$ 0·37, $MgSO_47H_2O$ 0·2, $NaHCO_3$ 2·1, glucose 1·0).

Results

The magnitude of the tension induced in the two preparations by 40 mM KCl ranged from 0·15 to 0·3 g for the hepatic portal vein and from 0·8 to 1·75 g for the aorta. In both tissues propofol concentrations from 1×10^{-6} M to 1×10^{-3} M produced a concentration-dependent relaxation up to a maximum of 100%. When doses of intralipid (propofol vehicle) alone were added, in concentrations corresponding to those associated with the maximum doses of propofol used in the study, no change in KCl induced tone was produced in either preparation.

Pilot studies indicated that the cycle times of 5 min for the vein and 25 min for the artery were appropriate to allow a steady state maximum relaxation to any given dose of the drug. These cycle times were used to obtain traces such as that shown in Fig. 1 for vein; similar traces were also obtained for artery. Accumulated data from such traces (two per preparation) were used to construct two curves (Fig. 2) representing the log concentration-

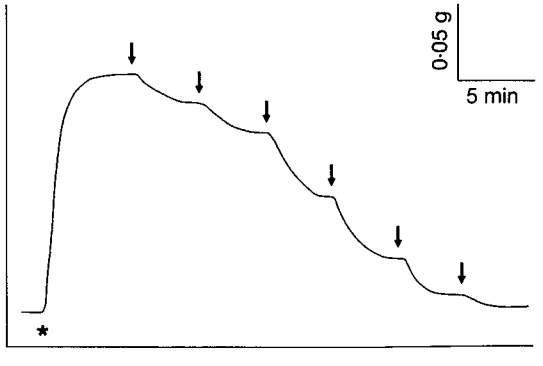

FIG. 1. The recorded changes in tension of an hepatic portal vein ring in response to the addition of KCl (40 mM;*) and propofol (↓). Arrows indicate the application of doses of propofol producing bath concentrations of (M): 1×10^{-6}; 3×10^{-6}; 1×10^{-5}; 3×10^{-5}; 1×10^{-4}; 3×10^{-4}.

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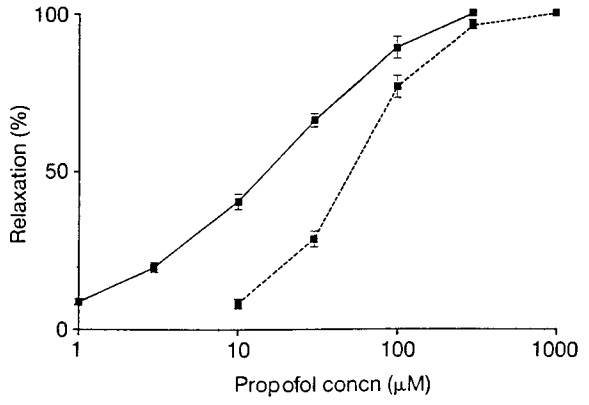

FIG. 2. Percentage relaxation of hepatic portal vein (solid line) and aorta (broken line) by propofol. Means ± s.e.m. were determined from the results of eight experiments from four preparations for each curve.

response (percentage relaxation) relationship for hepatic portal vein and aorta. These curves show that the hepatic portal vein responded to significantly lower propofol concentrations than did the aorta.

Discussion

This study has confirmed that propofol causes a direct relaxation of both venous and arterial tissue with the venous effects occurring at a lower propofol concentration.

Although the full range of propofol concentrations which occur clinically in man was studied here, our investigation falls short of providing conclusive evidence that these direct vascular effects occur clinically; it may not be possible to equate a dose of propofol which produces vascular relaxation in the rat with an equivalent anaesthetic dose in man.
Reasons for this are threefold:

(i) differences in vascular responses and in sensitivity may exist between rat and man, and also between isolated vessels and vessels in-vivo;
(ii) this investigation takes no account of the plasma protein binding of propofol which clinical studies have suggested may be of the order of 97–98% (Kirkpatrick et al 1988);
(iii) the concentrations of propofol which reverse KCl induced tone may not necessarily be the same as those which are required to counter the tone of physiological origin present in the whole animal.

All of these points, apart from possible species differences between animal and man, are accounted for in the anaesthetised dog preparation investigated by Goodchild & Serrao (1989). When considered together, the results of this investigation and the Goodchild & Serrao study indicate that sedative and anaesthetic levels of propofol in man cause venodilatation. This effect would cause an increase in capacitance and decrease in venous return to the heart in addition to and at the same time as the decreases in arterial and venous tone which are always encountered when anaesthesia is induced with any agent. This extra venous effect probably accounts for the greater reported falls in blood pressure and cardiac output associated with propofol anaesthesia compared with those occurring during anaesthesia with althesin (Cummings & Spence 1985), thiopentone (Grounds et al 1985) or methohexitone (Mackenzie & Grant 1985).

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