

POSTER SESSION XI

A553

TITLE: PROPOFOL PRODUCES VASODILATION BY A CALCIUM CHANNEL ANTAGONIST ACTION
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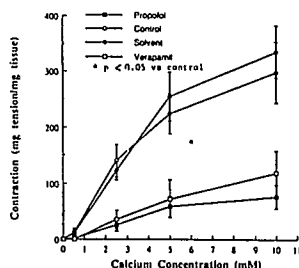
Vascular smooth muscle contracts when exposed to KCl because the KCl depolarizes cell membranes and opens voltage gated Ca²⁺ channels (VGCC) to permit the Ca²⁺ influx that produces contractions. No contraction results from KCl when the bathing solution is Ca²⁺ free, but incremental addition of Ca²⁺ produces incremental contraction strength. This protocol was undertaken to test the hypothesis that the vasodilation produced by propofol (P) involves inhibition of the influx of extracellular Ca²⁺ through VGCC in KCl depolarized aortic rings.

Segments of thoracic aorta (3 mm width) were obtained from male Sprague-Dawley rats, suspended in an organ bath in Krebs-Henseleit solution (KHS)(37°C), and aerated with 95% O₂/5% CO₂. Contractions were recorded isometrically using 2g resting tension. The concentration of P and verapamil (V) that produced 50% relaxation (IC₅₀) of the KCl (40 mM) induced contractions in this preparation, were 3 x 10⁻³M for P and 10⁻⁷M for V. The aortic rings were exposed to Ca²⁺ free KHS for 60 min and then incubated further with the IC₅₀ of P and V and with the P solvent (intralipid 10%) for another 20 min. In control preparations, an equal volume of distilled water was added. The preparations were then depolarized with KCl, 40mM for 10 minutes. Finally Ca²⁺ (as CaCl₂) was added to obtain final bath Ca²⁺ concentrations of 0.5, 2.5, 5.0 and 10 mM. DATA are expressed as MEAN ± SEM. ANOVA and Duncan's test were used to determine significance p < 0.05.

Aortic rings exposed to Ca²⁺ free media for 60 minutes failed to contract in response to 40 mM KCl. Reintroduction of Ca²⁺ to the bath produced dose dependent contractions, which were significantly attenuated in the aortic rings treated with either P or V compared to those treated with intralipid or control (Fig. n=6 in each group). There was no difference in Ca²⁺-response between control rings and those treated with intralipid. Nor was there a difference between the P and the V treated groups.

Thus, P decreases the contractile response elicited by incremental addition of Ca²⁺ to aortic rings depolarized by KCl in Ca²⁺ free solutions. The effect is similar to that produced by V. Because KCl induced contractions are due to influx of extracellular Ca²⁺ through VGCC, we conclude that propofol, like verapamil, inhibits extracellular Ca²⁺ influx through VGCC. The IC₅₀ of P for this response (30 μM = 6.9 μg/ml) is within the clinically useful range. Thus, the hypotension that sometimes accompanies clinical use of propofol may be, at least in part, caused by this Ca²⁺ channel blockade.

1. Ann Rev Pharmacol Toxicol, 24:175-197, 1984.
2. J Pharmacol Exp Ther 240:594-601, 1987.



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TITLE: MYOCARDIAL DEPRESSANT EFFECT OF PLASMA FROM LIVER TRANSPLANTED PATIENTS WITH POST REPERFUSION SYNDROME: AN IN VITRO STUDY
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Major cardiovascular changes occur during adult orthotopic liver transplantation (OLT) (1). It is well known that the main problem of OLT is a profound cardiovascular collapse following the reperfusion of the grafted liver (2) occurring in 30 % of cases. Two major mechanisms seem to be responsible : first, vasodilation as shown by the decrease in systemic vascular resistances and second, negative inotropic effect. The aim of the study was to test the hypothesis that plasma from patients undergoing OLT with postreperfusion syndrome (PRS) exerts a depressant effect on intrinsic contractility in isolated cardiac papillary muscle.

Eight consecutive patients (45 ± 6 yrs) undergoing OLT entered the study after approval by our Ethics Committee. We collected two samples in the right atrium : 1) before surgical incision ; 2) at the reperfusion phase when the systemic blood pressure was the lowest during PRS. The mechanical in vitro study was conducted blindly on left ventricular papillary muscle from adult Wistar rats (3). After a one-hour stabilization period, three mechanical indices were calculated : a) Vmax, the unloaded maximum shortening velocity ; b) AF/s, the peak isometric active force normalized per cross-sectional area ; c) +dF/s, the positive peak of active force derivative normalized per cross-sectional area. Thereafter, 5 ml of either before surgical incision or PRS plasma were added to the medium and mechanical parameters were calculated at the peak of the depressant mechanical effect. The investigators were not aware after the nature of the additional plasma. Mechanical results before surgical incision and PRS are both expressed as percentage of change in comparison with the control set point measured before addition of plasma. All the results are expressed as mean ± SD. Statistical analysis was performed using Student's t test after analysis of variance. Only statistical significant is figured.

For all patients the decrease in mean arterial pressure ranged from 8 % to 33% (mean = 22 ± 11 %) during the PRS in comparison with pre- incision hemodynamic data (p<0.05). The lead dependence of relaxation was markedly decreased in PRS.

Table: Percentage of change in comparison with control value before addition of plasma

mean ± SD	Vmax	AF/s	+dF/s
before surgical incision	- 10 ± 3	- 10 ± 2	- 7 ± 4
PRS	- 32 ± 5 ** \$	- 36 ± 12 \$\$	- 38 ± 10 *\$

\$, p<0.05 ; \$\$, p<0.02 vs control set point
 * p< 0.02, ** p<0.01 vs before surgical incision.

This in vitro study shows that PRS plasma induces a marked fall in intrinsic myocardial contractility. This demonstrated that liver transplanted patients have a circulating myocardial depressant substance in their blood during the postreperfusion phase.

References :

- 1) Transpl Proceeding , 21 : 3500-3505, 1989.
- 2) Transpl Proceeding , 19 : 54-55, 1987.
- 3) Amer.J.Physiol, 250 : 1008-1016, 1986.