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HAEMODYNAMIC CHANGES DURING ANAESTHESIA INDUCED AND MAINTAINED WITH PROPOFOL

M. A. CLAEYS, E. GEPTS AND F. CAMU

SUMMARY

The haemodynamic effects of propofol, given as a single dose of 2 mg kg^{-1} immediately followed by a continuous infusion of 6 mg kg^{-1} h^{-1}, were studied in 10 elderly patients premedicated with lorazepam 1 mg i.v. All patients breathed room air spontaneously. Unconsciousness was successfully induced in all patients and persisted during the 60 min of the infusion. Statistically significant decreases in systolic and diastolic arterial pressures were observed 2 min after induction (28% and 19%, respectively) and during infusion (30% and 25%, respectively) and were related to decreases in systemic vascular resistance (21% following induction and 30% during infusion). Cardiac output was not affected at any time nor were stroke volume and heart rate. We conclude that the arterial hypotension associated with the induction and infusion of propofol is mainly a result of a decrease in afterload without compensatory increases in heart rate or cardiac output.

Propofol (2,6 diisopropylphenol) is a potent hypnotic currently formulated as an oil-in-water emulsion. Its pharmacokinetic profile suggested that anaesthesia could be induced and maintained by a continuous infusion of the drug [1–3]. Indeed, a number of groups have reported on the use of an infusion of propofol alone [4] or in combination with regional analgesia [5, 6], opioids [7, 8] or nitrous oxide [9–12].

In patients premedicated with morphine 0.15 mg kg^{-1} the surgical ED_{50} for propofol given by constant infusion in association with 67% nitrous oxide was 54 μg kg^{-1} min^{-1} [13]. The reliable hypnotic activity of propofol suggests that it might be suitable as an alternative to nitrous oxide, etomidate or benzodiazepines for the maintenance of unconsciousness during analgesia-supplemented anaesthesia.

Although previous studies reported decreases in arterial pressures, no detailed studies of the cardiovascular and haemodynamic effects of the infusion of propofol alone in the absence of surgical stimulation are available. We have studied the haemodynamic effects of propofol administered as a 2-mg kg^{-1} bolus followed by a constant rate 6-mg kg^{-1} h^{-1} infusion exclusive of any other anaesthetic drug and in the absence of surgical stimulation.

PATIENTS AND METHODS

The study included 10 patients (ASA II, III; aged 50–75 yr) scheduled for total hip replacement without clinical evidence of cardiac or hepatic dysfunction. The demographic details of the study group are summarized in table I. Only one patient had a history of arterial hypertension. No other patients were in receipt of concurrent medication.

The study was approved by the University Ethical Committee and informed consent was obtained from each patient. All patients had received glycopyrrolate 0.4 mg i.m. 1 h before the study. A slow infusion of 5% glucose in lactated Ringer's solution was administered i.v. to replace insensible fluid loss and lorazepam 1 mg was

TABLE I. *Demographic data of patients (mean values ± SD)*

Age (yr)	62.4 ± 7.6
Weight (kg)	72.1 ± 14.7
Height (cm)	168.5 ± 4.9
Body surface (m^2)	1.82 ± 0.17

M. A. CLAEYS, M.D.; E. GEPTS, M.D.; F. CAMU, M.D.; Department of Anaesthesiology, Academisch Ziekenhuis, Flemish Free University of Brussels, Brussels, Belgium.
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injected i.v. as further premedication 40 min before the haemodynamic assessments.

Following the infiltration of local anaesthetic, a cannula (20 gauge) was inserted to the radial artery of the non-dominant arm to allow monitoring of arterial pressure, and a balloon-tipped thermodilution catheter (Edwards Laboratories) was placed in the pulmonary artery under continuous pressure control via the right internal jugular vein. ECG, heart rate, central venous pressure (CVP), systemic arterial and pulmonary artery pressures (systolic, diastolic and mean) were monitored continuously. All manipulations of the patient ended 20 min before baseline values were measured and any stimulation was avoided during the 60 min required for the haemodynamic evaluation. Following baseline measurements, unconsciousness was induced with propofol 2 mg kg^{-1} injected over 30 s. Simultaneously, a zero-order infusion of propofol was started at a rate of 6 mg kg^{-1} h^{-1} lasting 60 min and maintaining unconsciousness. All patients were allowed to breathe room air spontaneously. Special attention was paid to airway patency and the occurrence of apnoea and its duration; an oropharyngeal airway was inserted when needed. In seven patients arterial blood-gas analysis was performed before induction and after 45 min of infusion to evaluate blood-gas exchange.

Haemodynamic measurements were obtained before, and at 2, 6, 10, 15, 20, 30, 45 and 60 min after the initial administration of propofol and included determinations of heart rate, pulmonary artery pressures, pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), systolic (SAP) and diastolic (DAP) arterial pressures and cardiac output (CO). The pressure values were referenced to the level of the right

TABLE II. *Measured and calculated haemodynamic variables (mean ± SD). Differences from control*: *P < 0.05; **P < 0.01; ***P < 0.001

	Time (min)				
	0	2	6	10	15
SAP (mm Hg)	136±17	99±22***	93±18***	94±18***	92±18***
DAP (mm Hg)	66±10	53±15**	50±12***	50±12***	48±10***
HR (beat min^{-1})	74±18	81±10	77±11	74±12	73±12
SPAP (mm Hg)	23±6	25±9	25±7	24±5	24±5
DPAP (mm Hg)	10±6	11±6	10±5	10±4	10±3
SVR (dyn s cm^{-5})	1070±265	846±300***	792±270***	767±232***	761±250***
PVR (dyn s cm^{-5})	76±38	103±61*	95±47*	85±45	86±39
CO (litre min^{-1})	6.6±1.0	6.1±1.0	6.3±1.0	6.4±0.7	6.4±0.8
SV (ml $beat^{-1}$)	93±26	77±17	83±17	88±17	90±18
CVP (mm Hg)	6.4±3.8	5.1±3.0	5.4±2.9	5.4±2.6	5.4±2.5
PCWP (mm Hg)	9.7±3.8	8.3±3.2	8.4±3.2	8.7±2.8	8.5±2.8
RPP (mm Hg beat min^{-1})	9945±2304	7880±1205*	7104±1035***	6866±1387***	6588±1393***
LVSW (g m $beat^{-1}$)	120±46	72±27***	76±27***	79±28***	78±26***
RVSW (g m $beat^{-1}$)	76±38	103±61*	95±47*	85±45	86±39

	20	30	45	60
SAP (mm Hg)	93±17***	93±17***	96±16***	101±20***
DAP (mm Hg)	48±10***	48±11***	50±10***	51±12***
HR (beat min^{-1})	73±12	73±11	72±10	72±10
SPAP (mm Hg)	23±5	23±5	23±4	24±4
DPAP (mm Hg)	10±4	9±3	9±3	9±3
SVR (dyn s cm^{-5})	776±220***	748±260***	748±272***	775±275***
PVE (dyn s cm^{-5})	90±33	82±33	80±35	78±33
CO (litre min^{-1})	6.4±0.9	6.5±1.0	6.7±1.2	6.5±1.1
SV (ml $beat^{-1}$)	90±20	93±22	94±21	92±21
CVP (mm Hg)	5.5±2.5	5.6±2.8	5.5±2.8	5.7±2.9
PCWP (mm Hg)	8.6±3.1	8.5±2.7	8.3±2.9	8.6±3.0
RPP (mm Hg beat min^{-1})	6732±1506***	6695±1501***	6896±1405***	7276±1633***
LVSW (g m $beat^{-1}$)	79±28***	82±29***	85±16***	84±26***
RVSW (g m $beat^{-1}$)	90±33	82±33	80±35	78±33

atrium and recorded at end-expiration. Cardiac output (thermodilution) was determined in triplicate, using 10 ml of 5% dextrose in water at room temperature, at the end-expiratory phase of the ventilatory cycle. A mean value was calculated. Derived cardiovascular variables obtained using standard formulae included stroke volume (SV), systemic vascular resistance (SVR), left and right ventricular stroke work (LVSW, RVSW), rate–pressure product (RPP) and pulmonary vascular resistance (PVR).

All data are reported as mean values ± SD. Statistical analysis of the haemodynamic measurements included Student's t test with Bonferroni correction.

RESULTS

The mean values of the measured and calculated haemodynamic variables are presented in table II.

Pulmonary artery pressures, heart rate, cardiac output, CVP and PCWP did not change significantly at any time. Systemic arterial pressures (SAP, DAP) decreased rapidly and to a significant extent, by 28% and 19%, respectively, following the bolus injection of propofol, and by 30% and 25%, respectively, during the maintenance infusion ($P < 0.001$). These changes were accompanied by significant decreases in SVR on induction (−22%) and during infusion (−31%) ($P < 0.001$). The RPP remained decreased during the whole period of the study ($P < 0.001$). PVR increased by 36% ($P < 0.05$) immediately following the induction of unconsciousness, but was no more significantly affected during the infusion. SV decreased slightly 2 min after induction, and then returned gradually to baseline values. RVSW seemed unaffected, while LVSW decreased immediately by 39% ($P < 0.001$), following the bolus injection of propofol and remained 30% ($P < 0.001$) less than the control value during the infusion.

All 10 patients were helped by the placement of an oropharyngeal airway after induction, and in two patients its removal appeared necessary during the infusion period. Apnoea was noted in eight patients on induction of unconsciousness and lasted 90 ± 28 s (range 40–120 s). Arterial blood-gas analysis at 45 min indicated moderate respiratory impairment. pH values decreased from 7.38 ± 0.04 (control) to 7.30 ± 0.06 ($P < 0.01$) while Pa_{CO_2} increased from 5.07 ± 0.38 kPa (range 4.40–5.60 kPa) (control) to 5.66 ± 0.69 kPa (range 4.80–6.80 kPa) ($P < 0.01$).

DISCUSSION

The results of this study confirm the reported haemodynamic effects of an induction dose of propofol given as a single i.v. injection [9, 14–16] (table III) and are comparable to those found for other i.v. anaesthetics [17]. Apart from the initial tachycardia, similar changes were produced following the induction of anaesthesia with equipotent doses of thiopentone [16] and methohexitone [12].

During the maintenance of anaesthesia with an infusion of propofol (supplemented by nitrous oxide in oxygen) (table III), haemodynamic values similar to those obtained in the present study (except for the increase in HR) were observed, under comparable conditions, with Althesin [18], minaxolone [19], methohexitone [12, 20, 21] and thiopentone [22, 23].

Our results, obtained during the infusion of propofol in patients breathing room air, did not confirm the further decrease in arterial pressure and cardiac output reported by Prys-Roberts and colleagues [9], Coates and co-workers [14] and Monk and associates [15] (table III). These discrepancies can be explained to some extent by differences in methodology. The different haemodynamic response to propofol in the presence of nitrous oxide might be a result of the cardiovascular actions of the inhalation anaesthetic. Inhalation of a nitrous oxide–oxygen mixture produced a 15–20% reduction of cardiac output [24] as a result of decreases in HR and contractility, and an increase in SVR.

As reported in previous studies, we observed no significant change in heart rate during induction with, or infusion of, propofol. Normally, arterial baroreceptors regulate arterial pressure by modifying heart rate and systemic vascular resistance. The change in HR induced by the decrease of arterial pressure is variably affected by different i.v. induction agents. Anaesthesia with i.v. infusion agents depresses baroreflex sensitivity and resets the heart rate reflex set point to allow a more rapid heart rate at lower arterial pressures [25, 26], or a slower heart rate despite decreased arterial pressures [27]. The infusion of propofol during nitrous oxide in oxygen anaesthesia appears to induce marked resetting of the heart rate baroreflex set point to allow lower arterial

TABLE III. *Extent of haemodynamic changes induced by propofol as reported in the literature. The changes are expressed as percent difference from baseline value. *Statistically significant variations*

Authors/technique	HR	SAP	DAP	CO	SV	SVR	CVP	AWP	RPP	Premedication
Claeys (This study)										Lorazepam 1 mg i.v.
Bolus 2 mg kg^{-1}	+10%	−28%*	−19%*	− 7%	−17%	−21%*	−20%*	−14%	−22%*	Glycopyrrolate 0.4 mg i.m.
Inf. 6 mg kg^{-1} h^{-1}										
Spontaneous vent., no intubation, no N_2O	− 2%	−30%*	−25%*	− 2%	− 1%	−30%*	−13%	−12%	−31%*	
Coates [14]										Morphine 150 μg kg^{-1} i.m.
Bolus 2 mg kg^{-1}	+ 2%	−28%*	−12%	−14%	−13%	−17%	− 9%	—	—	Atropine 10 μg kg^{-1} i.m.
Inf. 6 mg kg^{-1} h^{-1}										
Intubation, 67% N_2O	− 7%	−45%*	−35%*	−26%	−20%	−22%	−11%	—	—	
Spontaneous vent.										
Prys-Roberts [9]										Morphine 150 μg kg^{-1} i.m.
Bolus 1.5 mg kg^{-1}	=	−21%*	−16%	−12%	−12%	− 9%	—	—	−24%*	Atropine 10 μg kg^{-1}
Inf. 3 mg kg^{-1} h^{-1}										
Intubation, 67% N_2O	− 9%	−31%*	−28%*	−19%*	−11%*	−17%*	+66%*	—	−38%*	
Spontaneous vent.										
Monk [15]										Morphine 150 μg kg^{-1} i.m.
Bolus 2 mg kg^{-1}	=	−29%*	−22%*	−13%	−11%	− 6%	—	—	—	
Inf. 3.2–3.9 mg kg^{-1} h^{-1}										
Intubation, 67% N_2O	−14%	−47%*	−31%*	−31%*	−18%	−11%	—	—	—	
Spontaneous vent.										
Grounds [16]										Papaveretum 15–20 mg i.m.
Bolus 2.5 mg kg^{-1}	=	MAP: −32%		−12%*	−14%*	−21%*	− 9%	—	−29%*	Hyoscine 0.3–0.4 mg i.m.

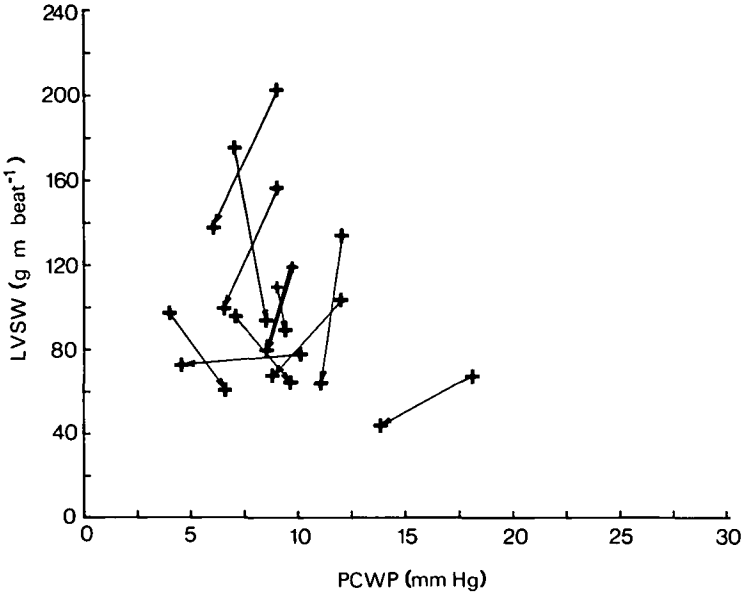

FIG. 1. Changes in left ventricular function during infusion of propofol. Arrows indicate changes between the measurement before propofol administration and the average value calculated from 10–60 min of propofol infusion for each patient. The thick arrow represents the mean for all patients.

pressures without tachycardia. Thus propofol may be regarded as exerting a central vagal predominance (or sympatholytic effect, or both).

In contrast to other i.v. anaesthetics, no depression of the baroreflex sensitivity was observed during the infusion of propofol (Prys-Roberts, personal communication, 1987). The baroreflex control of the SVR was markedly attenuated during the infusion and resetting of the reflex occurred to allow lower SVR for a given arterial pressure. The alteration of the baroreceptor reflexes suggests a direct vasodilating property of propofol on vascular smooth muscle, associated with a central depression of sympathetic outflow.

The absence of tachycardia with no significant decrease in CO is beneficial, since there is no increase in myocardial oxygen demand. The apparent absence of a myocardial depressant effect of the drug was confirmed by the maintenance of an adequate relation between LVSW and PCWP (fig. 1). Many have used RPP as an indirect index of myocardial oxygen demand [28]. In our study RPP decreased significantly after induction and during the infusion of propofol. However, the relevance of RPP is uncertain according to Reiz and colleagues [29] and Barash and co-workers [30].

The incidence and the duration of apnoea confirmed the greater ventilatory depressant effect of propofol observed by Grounds and colleagues [31] when compared with thiopentone. Dundee and co-workers [32] also reported more marked ventilatory depression in elderly patients. The significant increase in PVR at induction could result from hypoxic episodes during these apnoeic periods. During the infusion of propofol, the increase in Pa_{CO_2} confirmed the ventilatory impairment (see also references 9, 14, 15). Some cardiodepressive effects of propofol might have been masked in our study by the effects of the changes in Pa_{CO_2} on the cardiovascular system [33].

In conclusion, the major haemodynamic effect of propofol is a decrease in arterial pressure as a result of decreased SVR, rather than reduced SV or CO. In combination with other centrally vagotonic drugs, such as opioids, the resetting of the baroreflex set point may result in a slower HR and inadequate peripheral perfusion pressures, and has to be managed with care. The ventilatory impairment may limit the use of an infusion of propofol in spontaneously breathing patients.

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