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Cerebral Effects of Propofol Following Bolus Administration in Sheep

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SUMMARY

The effects of bolus administration of propofol (50 mg, 100 mg and 200 mg) on cerebral blood flow and cerebral metabolic rate for oxygen were examined in a chronically catheterized sheep preparation. Depth of anaesthesia was simultaneously measured using a withdrawal response to a noxious electrical stimulus and it was demonstrated that the 100 mg dose induced moderate sedation while the 200 mg dose induced relatively deep anaesthesia. Propofol caused transient dose-dependent decreases in cerebral blood flow, despite minimal changes in blood pressure. These were accompanied by parallel decreases in cerebral metabolic rate but no change in cerebral oxygen extraction. As cerebrovascular responses in the sheep appear similar to those in man, the parallel changes in cerebral blood flow and metabolic rate demonstrated in this study supports the suitability of propofol as a neuroanaesthetic agent.

Key Words: ANAESTHETICS, PHARMACOLOGY: propofol, cerebral blood flow, cerebral metabolism

Propofol, a substituted phenol, is a sedative/hypnotic agent which has increased in popularity in neuroanaesthetic practice in recent years. Its pharmacokinetic properties allow rapid increases in depth of anaesthesia in order to minimize responses to stimuli such as intubation and surgery, and intravenous infusion allows maintenance of stable depths of anaesthesia intra-operatively without prolonged recovery times. Its cerebral pharmacodynamic properties also appear suitable for neuroanaesthesia, with studies in human and animal subjects demonstrating propofol induced dose dependant decreases in cerebral blood flow (CBF), cerebral metabolic rate for oxygen (CMR) and intracranial pressure (ICP). Preservation of CBF-CMR coupling, an important property of neuroanaesthetic agents, is less clearly demonstrated. Most studies to date, although generally showing simultaneous decreases in CBF and CMR, have been performed using anaesthetized experimental preparations, and thus have only studied CBF and CMR effects at relatively deep planes of anaesthesia and often in the presence of anaesthetic agents which themselves alter CBF. Furthermore, the relative time-courses of CBF and CMF have been examined only during infusion administration of propofol and not during sedation or rapidly changing depths of anaesthesia.

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A chronically instrumented sheep preparation has recently been developed in which CBF, CMR and an index of depth of anaesthesia can be measured in otherwise unanaesthetized animals, and this was used to examine the effects of anaesthesia induced by bolus intravenous administration of propofol on these variables.

METHODS AND MATERIALS

Animal Preparation

All experimental protocols were approved by the Ethics Committees of the University of Adelaide and Institute of Medical and Veterinary Sciences (Adelaide). Female Merino sheep of similar ages and body mass were used, and animals were initially prepared according to the general method of Runciman et al (1984) under general anaesthesia[1]. For sampling of arterial blood and for measurement of arterial pressure, two 7F catheters (Multi-purpose A1 catheter, Cordis Corporation, Miami, Fl., U.S.A.), were placed in the carotid artery and positioned under radiographic control with their tips at the origin of the brachiocephalic trunk. One 7F catheter, for drug administration, was placed in the jugular vein and positioned with its tip in the right atrium. Catheters were fastened to the strap muscles of the neck using a small plastic plate and exteriorized.

A 19 mm trephine hole was made in the skull and a 1 mm diameter 20 MHz piezoelectric Doppler transducer (Titronics Medical Instruments, Iowa City, Iowa, U.S.A.) placed over the sagittal sinus for CBF measurement. A 4F catheter (Cook Incorporated, Blooming-

ton, U.S.A.), for sagittal sinus blood sampling, was inserted into the sagittal sinus approximately 1 cm rostral to the Doppler probe and positioned so the tip lay approximately 4 cm from the probe. The catheter and Doppler probe wire were exteriorized and the bone plug replaced. The sheep then recovered from anaesthesia and were housed in metabolic crates, with catheters continuously flushed with heparinized saline.

Experimental Design

Studies were commenced a week after surgery to allow wound healing. For each study sheep breathing room air remained in their metabolic crates with their weight partially supported by a sling. Cerebral blood flow, cerebral metabolic rate and depth of anaesthesia were measured in each study as described below.

Cerebral blood flow was measured using the venous outflow method of Upton et al[2], with a directional pulsed Doppler flowmeter (Bioengineering, University of Iowa, U.S.A.) connected to the sagittal sinus transducer, and using a sampling rate of 1 Hz. Upton et al showed that this method measures the velocity of approximately 70% of cerebral blood, predominantly that from the cerebral cortices, and that blood velocity correlated very closely with blood flow over a wide range of CBF values as a result of constant vessel cross-sectional area and the absence of turbulent flow. Because the Doppler signal therefore remains proportional to actual flow at all times it was considered unnecessary in this study to calibrate the Doppler signal against flow in each animal at the end of each series of experiments. The CBF was recorded as a percentage of baseline as slightly different probe placement in relation to the sagittal sinus in each animal produces a different Doppler output for any given flow. The flowmeter output was recorded using an analogue to digital card (Metrabyte DAS 16-G2) and a personal computer (Microbits 486-based IBM compatible).

To measure oxygen extraction (the difference between arterial and sagittal sinus oxygen contents), blood samples were taken from the arterial and sagittal sinus catheters at intervals for later analysis of gas tensions and oxygen content using a gas analyser (CIBA Corning 278, MA, U.S.A.) and an oximeter (IL482, Instrumentation Laboratory, Lexington, MA, U.S.A.) calibrated for sheep blood[3]. Cerebral metabolic rate was calculated from the product of cerebral oxygen extraction and Doppler output, and was recorded as a percentage of baseline for the reasons explained above.

The anaesthetic effect of propofol was measured at 30-second intervals using the method of Ludbrook et al[4]. In brief, a ramped pulsed electrical DC current was applied to the lower hind limb of the sheep through two subcutaneous 26 gauge needles using a modified peripheral nerve stimulator (Digistim 3, Neuro Technology, Houston, Texas, U.S.A.), and the current threshold required to produce limb withdrawal observed and recorded.

Blood pressure was measured via one of the arterial catheters connected to a pressure transducer and monitor (Hewlett-Packard model 78345A, Boeblingen, Germany) and recorded on the personal computer.

In each study, after the baseline variables were recorded for three minutes and baseline arterial blood samples taken, either 50 mg, 100 mg or 200 mg of propofol was administered intravenously over two minutes using a syringe pump (Model 33, Harvard Apparatus Ltd, Kent, England). All variables were recorded for 40 minutes and blood samples were taken from the catheters at 2, 4, 10 and 20 minutes from the commencement of propofol administration. Each dose was administered to five sheep, but because of probe or catheter failure, a total of eight sheep were studied. Two sheep received all doses in random order, three sheep received two doses and three sheep received only one dose. In sheep receiving more than one dose, at least 48 hours was allowed between studies.

Data Analysis

For CBF, the Doppler output in individual animals was averaged at 30-second intervals and expressed as a percentage of the average baseline values. Cerebral metabolic rate was calculated at each time point in individual animals from the product of the arterial-sagittal sinus oxygen content difference and the CBF, and expressed as a percentage of baseline. In each animal the ratio of CMR and CBF at each time point was then calculated. For measurement of depth of anaesthesia, the current threshold values at each time point in individual animals were expressed as a percentage of the average baselines values. Data at each time point for all animals were then pooled and expressed as mean and standard error of the mean (SEM). Changes in all variables were examined using repeated measures analysis of variance (ANOVA).

RESULTS

Cerebral blood flow decreased significantly following 50 mg, 100 mg and 200 mg of propofol ($P=0.002$, $P<0.0001$, $P<0.0001$ for each dose respectively). The 200 mg dose prolonged the duration of the CBF decrease but did not alter the magnitude of maximum decrease (Figure 1). These CBF changes were accompanied by small decreases in MAP, with maximal decreases of 9 mmHg, 11 mmHg and 7 mmHg after the 50 mg, 100 mg and 200 mg doses respectively, but the decrease was statistically significant only after the

200 mg dose ($P=0.43$, $P=0.47$, $P=0.002$ respectively). All doses of propofol produced significant respiratory depression. There was a transient increase in P_aCO_2 ($P=0.001$, $P<0.0001$, $P<0.0001$ for each dose respectively) with maximum increases of 0.93 kPa, 0.98 kPa and 1.41 kPa respectively (Figure 2). There was, however, no significant change in arterial oxygen content ($P=0.06$, $P=0.28$ and $P=0.07$ for each dose respectively; Figure 3).

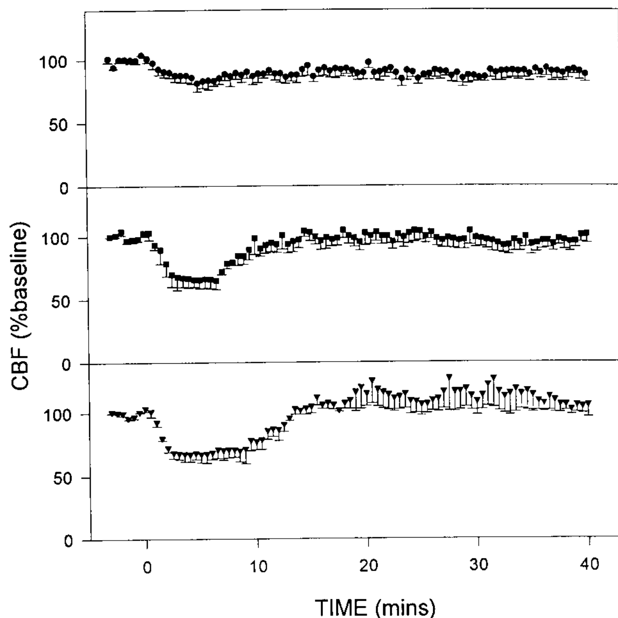

FIGURE 1: Changes in CBF over time following propofol doses IV over 2 minutes of 50 mg (circles), 100 mg (squares) and 200 mg (triangles). Mean±SEM.

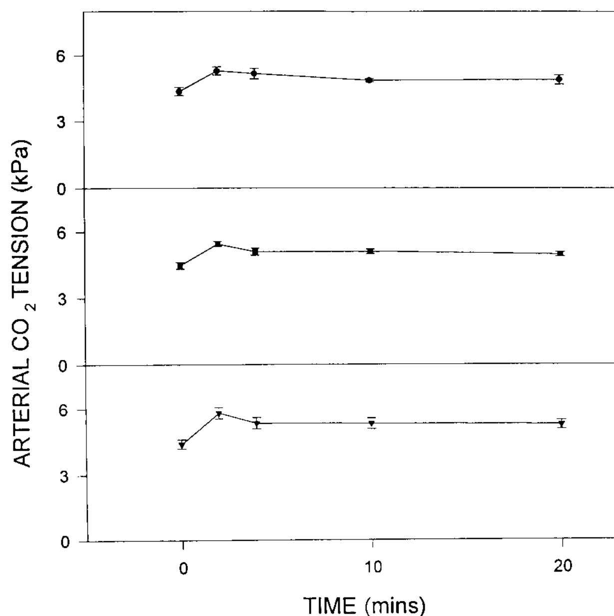

FIGURE 2: Changes in P_aCO_2 over time following propofol doses IV over 2 minutes of 50 mg (circles), 100 mg (squares) and 200 mg (triangles). Mean±SEM.

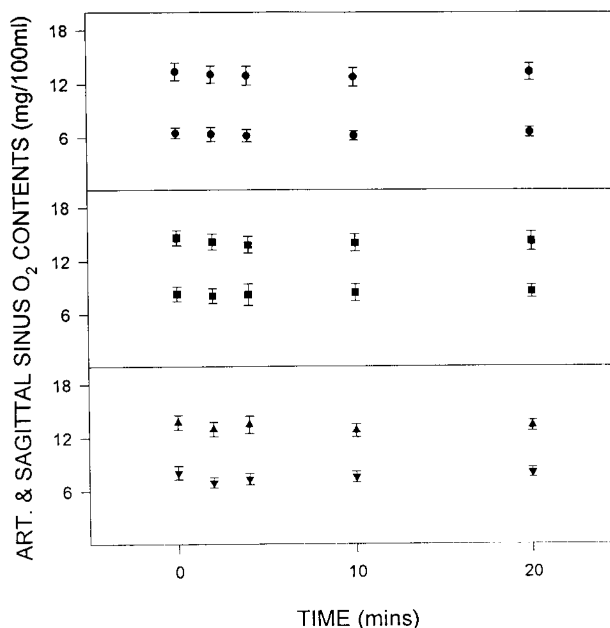

FIGURE 3: Oxygen content of arterial and sagittal sinus blood following propofol doses IV over 2 minutes 50 mg (circles), 100 mg (squares) and 200 mg (triangles). Mean±SEM.

There was no significant change in sagittal sinus oxygen content ($P=0.23$, $P=0.76$ and $P=0.28$ for each dose respectively; Figure 3) nor in oxygen extraction ($P=0.84$, $P=0.65$ and $P=0.51$ for each dose respectively).

Cerebral metabolic rate decreased following 50 mg, 100 mg and 200 mg of propofol ($P=0.007$, $P=0.059$ and $P=0.023$ for each dose respectively) but the decrease after the 100 mg dose failed to reach statistical significance at the 0.05 level. Changes in CBF and CMR followed a similar time-course following all doses (Figure 4) with no statistically significant change in the ratio of CBF-CMR over time ($P=0.81$, $P=0.66$ and $P=0.58$ after each dose respectively; Figure 5).

Current threshold changed significantly after all doses of propofol ($P=0.045$, $P<0.0001$ and $P<0.0001$ after each dose respectively) with a time-course of change similar to those of CBF and CMR. Increases in current threshold were closely and consistently accompanied by subjective signs of sedation and anaesthesia such as reduced spontaneous movement or eye closure. The increase was maximal (173%) at five minutes after 100 mg, but the maximum increase after 200 mg could not be quantified because no response occurred at the highest current levels deliverable (Figure 6).

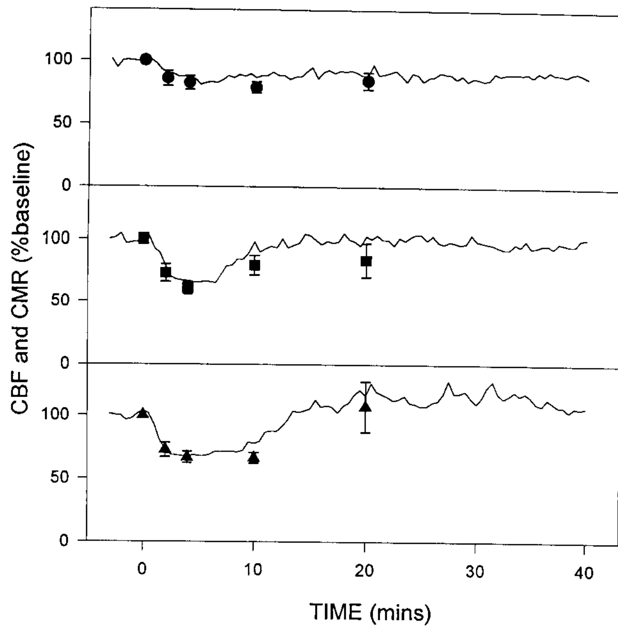

FIGURE 4: Changes in CMR (symbols) and CBF (lines) over time following propofol doses IV over 2 minutes of 50 mg (circles), 100 mg (squares) and 200 mg (triangles). Mean±SEM.

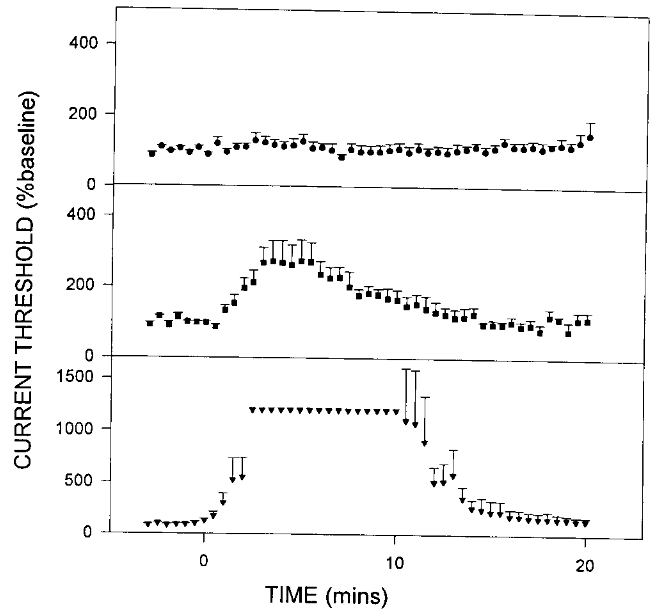

FIGURE 6: Current threshold over time following propofol doses IV over 2 minutes of 50 mg (circles), 100 mg (squares) and 200 mg (triangles). Mean±SEM. For the 200 mg dose maximum current levels were reached between 2.5 and 10 minutes and so current threshold could not be quantitated.

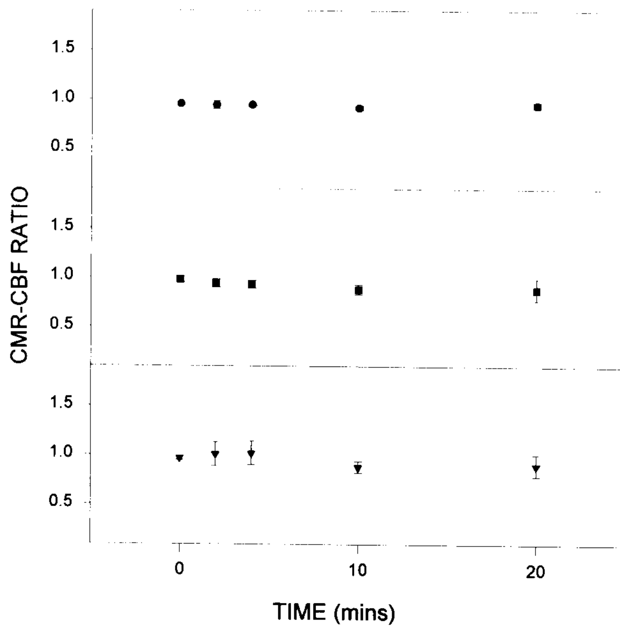

FIGURE 5: The ratio of CMR to CBF following propofol doses of 50 mg (closed circles), 100 mg (squares), 200 mg (triangles). Mean±SEM.

DISCUSSION

In many studies in the literature of the effects of propofol on CBF it is difficult to determine the influence of the concomitant anaesthetic agents on CBF. However, despite the use of a range of anaesthetic agents in experimental preparations, studies have consistently demonstrated a dose-dependant decrease in CBF in a number of species, with maximal recorded decreases approaching 50 to 70%[5-10]. These results are supported by the findings of the current study in which a dose-dependant reduction in CBF was demonstrated when propofol was administered alone. Although these drugs doses produced decreases in MAP, these were unlikely to have had a major influence on CBF because decreases were minimal (statistically significant only after the 200 mg dose) and, furthermore, reasonable preservation of cerebral autoregulation during propofol administration has previously been demonstrated[11,12]. This minimal effect on MAP even at anaesthetic doses of propofol is probably a result of the relatively slow bolus administration rate[13] and preservation of normal cardiovascular baroreceptor reflexes in an awake preparation.

Respiratory support was not possible when using this preparation, and subsequently there were dose-dependant significant changes in P_aCO_2 which had the potential to additionally influence CBF. Hypoxaemia has previously been shown to influence CBF only when Hb saturation falls below 80 to 90%[14] and, because arterial oxygen content did not change significantly, was unlikely to have affected recorded CBF values. The propofol induced changes on P_aCO_2 may, however, have affected CBF in this study. Hypercarbia has been shown to increase CBF in this sheep preparation under halothane anaesthesia[2] and previous

work in other animals suggests that the CBF response to CO_2 is preserved during propofol administration[10,15]. The experimental design in the current study did not permit control of P_aCO_2 because it involved rapid changes in conscious state from awake to anaesthetized. It was not, however, possible to accurately determine the effect of hypercarbia on the time-course of CBF changes. Although the longterm CBF response to changes in P_aCO_2 has previously been measured[16], a significant delay between the onset of hypercarbia and CBF changes has been demonstrated making accurate estimation of the immediate effect of hypercarbia on CBF difficult[17]. Furthermore, there may be an inconsistent relationship between CBF and hypercarbia immediately after CO_2 increases occur[18]. Hypercarbia may have contributed to the minimal difference in the peak CBF decrease observed following the 100 mg and 200 mg doses but accurate determination of the iosolated effects of specific drug doses on CBF and the maximum propofol-induced depression of CBF would require a separate protocol involving intubation and ventilatory support to maintain normocarbia during drug administration via infusion, and therefore would only be possible at relatively deep planes of anaesthesia and probably with pharmacological support of systemic arterial pressure.

Although decreases in both CBF and CMR following propofol have generally been demonstrated, in most studies propofol has had a relatively greater effect on CBF than CMR[5,6,7,19], and this has been attributed to both the concomitant use of other anaesthetic agents such as volatile agents and the presence of significant decreases in systemic arterial pressure in anaesthetized animals. Close coupling of CBF and CMR was recorded in rabbits during propofol administration when N_2O-morphine rather than volatile anaesthesia was used and when normotension was maintained with angiotensin[8].

These findings are consistent with those in the current study in which, as shown in Figure 4, a close relationship between the time-course and magnitude of changes in CBF and CMR both during onset and offset of anaesthesia was demonstrated. Furthermore, the lack of change in oxygen extraction over time adds further support to the hypothesis that oxygen delivery remained coupled to cerebral metabolic requirements during propofol administration, as there is some evidence that oxygen extraction changes occur when CBF is unmatched to cerebral metabolic needs[20]. Although not statistically significant, the trend towards more rapid recovery in CBF after drug administration was ceased, shown in Figure 4, may represent a differential effect of hypercarbia on CBF rather than CMR[21,22].

The use of a withdrawal response to a noxious stimulus is a concept similar to that previously used to determine anaesthetic effect of drugs[23] and provided a functional measurement of sedative-hypnotic effects somewhat analogous to that required in clinical practice. It was sufficiently sensitive to permit detection of changes in the sedative effects of propofol prior to that allowed by observation of subjective measures of sedation and anaesthesia such as reduction in spontaneous movements, eye closure and postural changes, and the consistent relationship between the time-course of changes in current threshold and these subjective measures suggests that this method is both reliable and reproducible.

Although it is difficult to equate an electrical current delivered to a sheep with surgical stimuli, our experience has been that an increase in current threshold of 200 to 300% (an increase achieved at a dose somewhere between the 100 mg and 200 mg doses in the current study) corresponds to a depth of anaesthesia sufficient to allow laryngoscopy and endotracheal intubation without the use of muscle relaxants. Thus the observed maximal decreases in CBF and CMR of approximately 35% recorded in the current study at these depths of anaesthesia are consistent with published work referred to previously. This technique therefore appears valuable because it allows measurement of the degree of propofol-induced sedation or light anaesthesia corresponding to the CBF and CMR changes induced by each drug dose. Other methods of measurement of propofol-induced depth of anaesthesia such as electroencephalography are relatively impractical in an awake or lightly sedated animal, but do allow measurement of propofol-induced suppression of cerebral electrical activity at deep planes of anaesthesia when any withdrawal response has been ablated[8]. Although application of any stimulus may induce agitation and thus alter CBF it is unlikely that this occurred in the current study. Validation of this method[4] revealed no change in behaviour of the animals unless measurements were made almost continuously (approximately every 10 seconds). Furthermore, in the pre-baseline period at the start of each experiment CBF measurements were commenced first and no change in CBF was noted once application of the current was started.

Although this study was conducted in sheep, all other studies using this preparation have demonstrated that cerebrovascular responses in this species are similar to those reported in other species, including man. Both the CBF response to CO_2 and the absolute flow per brain mass are similar to other work[2]. Furthermore, unpublished data from this laboratory have demonstrated preservation of cerebral autoregulation and

CBF responses to vasoactive pharmacological agents such as sodium nitroprusside, metaraminol and volatile anaesthetic agents consistent with data in other species, including man.

The results from this study therefore support the previous findings that propofol administration in sheep produces a dose-dependant decrease in CBF independent of changes in MAP, and that CMR-CBF coupling is preserved during sedation as well as during deep planes of anaesthesia. These data therefore support the suitability of propofol as a neuroanaesthetic agent.

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