Efficacy of intracarotid propofol infusion and impact of cerebral blood flow alteration†

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Background. Intracarotid propofol infusion was studied in canines as an experimental basis for application of propofol in the Wada test.

Methods. First, efficacy and side-effects of propofol anaesthesia were studied in eight mongrel dogs that received intracarotid and i.v. propofol infusions for 30 min according to a cross-over design. Auditory evoked potentials were used to guide anaesthesia. Secondly, eight mongrel dogs received intracarotid propofol infusion during both normal and cerebral hyperperfusion states using nicardipine. Haemodynamics and clinical endpoints were compared between the two infusion conditions.

Results. We required 33 (7.6) mg propofol intracarotically vs 113 (17) mg propofol i.v. to achieve an anaesthetic state. The mean arterial pressure (MAP) decreased about 15–27% from the baseline during i.v. infusion. However, no obvious decrease of MAP was observed after intracarotid infusion. Administration of nicardipine increased the blood flow in the internal carotid artery by 17%. Then, the propofol dosage for achieving the anaesthetic effect increased from 7.7 (0.9) mg in the normal control to 11.3 (0.8) mg in the nicardipine group. The onset time of anaesthetic effect was prolonged and the recovery time was shortened during intracarotid infusion during cerebral hyperperfusion.

Conclusions. Compared with i.v. propofol infusion, intracarotid infusion could reach and maintain the target anaesthetic depth with less dosage and without affecting MAP. In addition, increase of cerebral blood flow requires a higher propofol dose, prolongs onset, and shortens recovery time during intracarotid propofol anaesthesia, indicating that patients with a cerebral hyperperfusion state may need higher dose of anaesthetics during the Wada test.


Keywords: anaesthetics i.v., propofol; brain, blood flow; drug delivery, infusion; monitoring, depth of anaesthesia

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The Wada test has been widely used to determine language and memory lateralization in neurosurgical candidates, especially in patients with refractory epilepsy.¹ The basic methodology of the test consists of a bolus injection of a barbiturate for brief anaesthesia of two hemispheres one after another. During this short anaesthesia, a simple speech and memory tests are executed. Although amobarbital has been commonly used for this purpose, it is not available in many countries. Furthermore, the effect of amobarbital is usually completely dissipated after about 6–8 min with the full effect lasting only about 3 min when the drug is injected into the carotid artery.² ³ This might be a problem for those using lengthy memory or language testing during the Wada test. Attempts have been made to find alternative anaesthetic agents. Several studies have evaluated the usefulness and safety of propofol, a widely available anaesthetic agent, to perform the Wada test.⁴ ⁵ These results suggest that the traditionally used amobarbital could be replaced by propofol in the Wada test as no severe side-effects were observed. However, because only a small number of human subjects and a bolus injection of propofol were

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used in those studies, the efficacy and safety related to propofol intracarotid infusion need to be revealed in further preclinical investigations.

We hypothesized that a specific anaesthetic depth could be achieved and maintained for longer time by means of intracarotid propofol continuous infusion. If this new procedure was introduced into the Wada test, we may easily control the duration of hemi-anaesthesia and optimize the dosage of anaesthetic agent according to the testing requirement. We tested this hypothesis in mongrel dogs. Since in canine we cannot perform speech and memory tests, the specific anaesthetic depth to meet the test demand was monitored by the mid-latency auditory evoked potential (MLAEP) monitor (A-Line, Dannmeter, Odense, Denmark) in reference to the response of the tail clamping test. In this study, we first investigated the efficacy of an intracarotid propofol infusion at a specific targeted anaesthetic depth through comparison with a traditional i.v. administration. Secondly, since ictal or interictal single-photon emission CT have revealed that cerebral perfusion abnormalities occur in most patients with refractory epilepsy, we then evaluated whether the perfusion abnormalities affect the anaesthesia of the Wada test by observation of the effect of a cerebral blood flow (CBF) increase induced by the administration of nicardipine, a vasodilator agent, on the efficacy of intracarotid propofol infusion.

Methods
The experimental protocol used in this study was approved by the Ethics Committee for the Animal Experimentation of the Fourth Military Medical University and was conducted according to the Guidelines for Animal Experimentation of the university. The experiments were done at the Stomatological College, Fourth Military Medical University, Xi’an, People’s Republic of China.

Animals and preparation
The study was conducted on male healthy mongrel dogs (18–20 kg). All the animals were deprived of food for 12 h and water for 6 h before the experiment. First, the animals were anaesthetized with isoflurane 3% (Astra Zeneca Pharmaceuticals, UK) inhalation through a mask. The left brachiocephalic vein and the left femoral vein were cannulated with a paediatric multi-lumen central venous catheter. The left common carotid artery, cranial artery, and caudal thyroid artery were ligated.

Under local anaesthesia [bupivacaine 0.25% (containing 1:200 000 epinephrine)], the left common carotid artery was dissected through a median incision in the neck and cannulated with a paediatric multi-lumen central venous catheter. The left external carotid artery, cranial artery, and caudal thyroid artery were ligated.

The MLAEP were recorded using the A-line® monitor (version 1.4; Dannmeter A/S). For this purpose, three steel needle electrodes were placed subdermally under local infiltration anaesthesia. The positive electrode was placed 3 cm in front of the intersection of the median sagittal line and biauricular line; the negative electrode was placed at left mastoid; and the reference electrode was positioned 1 cm above the line between positive and negative electrodes. Electrode impedance was accepted if <5 kΩ (default settings). The MLAEP was elicited by bilateral click stimuli at 70 dB intensity and 2 ms duration. The A-line ARX index (AAI) was calculated from the MLAEP as described elsewhere.7

To measure the blood flow through the internal carotid artery (ICA), the left common carotid artery was encircled by an electromagnetic flowmeter (Nihon Kohden, Japan). Data obtained from the flowmeter reflect the flow in ICA since other branches from the common carotid artery had been ligated as described above. Indeed, cerebral arterial vascularization is provided by a large anastomatic network for which we cannot control by only ligaturing the extracranial afferences from the external carotid supply. However, we believe that this theoretical limit might have moderate impact on the results. Isoflurane inhalation was terminated as all the preparations were completed.

Determination of AAIawake and AAIhypnotic
The AAI in each dog was recorded every 5 min three times and the AAIawake of the dog was calculated by averaging the data. Subsequently, the AAIhypnotic for each dog was measured. Propofol was infused via the femoral vein at the rate of 2 mg kg⁻¹ min⁻¹ until the lash reflex disappeared and then the tail clamping test was carried out. A padded sponge clamp was placed on the tail at a point where the circumference of the tail was about 9 cm. The clamp was closed to full rachet and maintained for 60 s. Tail clamping test was repeatedly done once a minute and if the dog responded, propofol 10 mg was injected. A positive response to the tail clamping was considered to be a gross purposeful muscular movement in the head or other extremities. Only significant jerking or twisting motions were recognized as responses, but not head movements such as twitches or grimaces. Coughing, swallowing, and chewing were also not considered to be positive responses. The values of AAI at the time when the dog did not respond to the tail clamping were recorded. Such tests were repeated three times in each dog and the AAIhypnotic was calculated by averaging those three AAI
values. The second and third measurements were carried out once AAI increased to 95% of the AAI_{awake}.

**Preliminary experiment to determine the intracarotid infusion rate of propofol**

A preliminary experiment was performed to determine the suitable rate for intracarotid infusion of propofol. Three healthy mongrel dogs received an isoflurane inhalation anaesthesia for common carotid artery cannulation. Once the AAI value of each dog increased to 95% of their AAI_{awake}, intracarotid infusion of propofol started at the rate randomly chosen at 0.1, 0.2, and 0.5 mg kg\(^{-1}\) min\(^{-1}\). Infusion was stopped when AAI reached the AAI_{hypnotic}. Intracarotid infusion at each rate was cycled three times in each dog. Recovery of AAI from AAI_{hypnotic} to 95% of AAI_{awake} was the prerequisite of the beginning of another cycle. The time to reach AAI_{hypnotic} was recorded.

We finally determined to choose a propofol infusion rate of 0.1 mg kg\(^{-1}\) min\(^{-1}\) for this experiment because at this rate, the time duration to reach the AAI_{hypnotic} was not too short for observation. There was not any behaviour disorder observed in the animals within a week after the preliminary experiment. However, a haematoma at the neck occurred in one dog. The dog finally survived after treatment including ligation of its left common carotid artery and clearance of the haematoma.

**Experiment 1: intracarotid vs i.v. propofol anaesthesia**

Eight healthy mongrel dogs weighing 15–20 kg received both intracarotid and i.v. propofol infusions one after another according to a cross-over design. When four of them received intracarotid infusion, the other four received i.v. infusion. Twenty-four hours later, the infusion method was exchanged in each dog.

For intracarotid infusion, diluted propofol (0.2%, i.e. an oil solution of propofol was dispersed in saline at a concentration of 10 mg per 5 ml) was infused constantly at the rate of 0.1 mg kg\(^{-1}\) min\(^{-1}\) using an infusion pump until AAI reached AAI_{hypnotic}. Then, the constant infusion was changed to intermittent infusion to keep AAI in the range of AAI_{hypnotic} (5). The procedure was ended when AAI was maintained in the above range for 30 min where-after the dog was allowed to recover.

For the i.v. infusion, propofol 1\% was administered at the rate of 2 mg kg\(^{-1}\) min\(^{-1}\) at the beginning and changed to 0.5 mg kg\(^{-1}\) min\(^{-1}\) during the intermittent infusion period. Other steps in the process were the same as those in the intracarotid infusion.

Blood was sampled at different time points before and during the infusion period for measurement of propofol concentration with high-performance liquid chromatography (HPLC). For HPLC assay, 500 \(\mu\)l of thymol, served as an internal control (1 \(\mu\)g ml\(^{-1}\) in acetonitrile), was added to 300 \(\mu\)l of sample plasma. After precipitation of protein with saturated ammonium sulphate and centrifugation for 5 min at 16 000 rpm, 20 \(\mu\)l supernatant was added into the column. The analytical column was a Diamonsil C18 column (250 mm length \(\times\) 4.6 mm ID and 5 \(\mu\)m in particle size, Dikma Company Inc., USA). The mobile phase consisted of acetonitrile–water (70:30, containing trifluoracetic acid 0.1%) delivered at 1 ml min\(^{-1}\). The excitation and emission wavelengths were 270 and 310 nm, respectively. A linear relationship was obtained between the peak-height ratio of propofol to thymol against the spiked concentration with coefficient of 0.9993 over the range of 0.1–10 \(\mu\)g ml\(^{-1}\). The detection limit of propofol was 50 ng ml\(^{-1}\). The average recovery was more than 90%. Both the intra- and the inter-day precisions were <4%.

Propofol dosage and recovery time (duration for AAI recovered from AAI_{hypnotic} to 95% of AAI_{awake}) of each dog for both intracarotid and i.v. infusion were recorded. MAP was noted down every 5 min during the maintenance of infusion. For propofol concentration measurement, blood was sampled before anaesthesia and at the time point when MAP was recorded. Possible animals’ behavioural changes were observed during the week after the experiment.

**Experiment 2: intracarotid propofol anaesthesia under cerebral hyperperfusion**

Eight healthy mongrel dogs received an intracarotid propofol infusion twice in different conditions. At the first occasion, a constant intracarotid infusion of diluted propofol (0.2%) was applied at the rate of 0.1 mg kg\(^{-1}\) min\(^{-1}\) until AAI reached AAI_{hypnotic}. Then the constant infusion was changed to an intermittent infusion to maintain AAI in the range of AAI_{hypnotic} (5). This infusion was ended when constant and intermittent infusion lasted for 15 min and then dogs were allowed to recover.

The second session of intracarotid infusion was performed under cerebral hyperperfusion state induced by nicardipine and esmolol administration. After the dogs recovered from the first intracarotid anaesthesia (AAI reached 95% of AAI_{awake}), nicardipine 0.01% (glucose 5% as dissolvent) was infused i.v. at an initial rate of 5 \(\mu\)g kg\(^{-1}\) min\(^{-1}\). The infusion rate was elevated gradually by steps of 0.5–10 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) in order to slowly induce a systemic hypotension but cerebral hyperperfusion. Intracarotid propofol infusion began once MAP decreased by one-third from baseline. The steps of intracarotid propofol administration were the same as those in the first session. A bolus of 5–10 mg esmolol was administered i.v. if heart rates increased by 20%. MAP was always maintained at a level less than two-thirds of the baseline value during the second intracarotid infusion.

The haemodynamic parameters and the ICA flow at pre-anaesthesia condition and at the time when AAI reached AAI_{hypnotic} were recorded. The dosage of propofol for two
intracarotid infusion, time to reach AAI{sub}hypnotic{sup}, and recovery time (duration of AAI recovered from AAI{sub}hypnotic to 95% of AAI{sub}awake) were recorded. Possible animals’ behavioural changes were observed during the week after the experiment.

Statistical analysis
The data are presented as mean (SD). The values of MAP and propofol concentration at different time points from Experiment 1 were normalized to the baseline value and analysed by repeated measures analysis of variance. The propofol dosage and recovery time in i.v. and in intracarotid artery anaesthesia in Experiment 1 were analysed using the variance analyses for two phases cross-over design. Data from two intracarotid anaesthesia occasions in Experiment 2 were compared using paired t-test. Statistical significance was set at \( P<0.05 \).

Results

Experiment 1
All the animals survived in the following week after experiment and no behavioural disorder was observed. We found that an intracarotid propofol infusion could achieve and maintain the desirable targeted anaesthetic effect during intracarotid infusion [33 (7.6) mg] was about one-fourth of that in i.v. administration [113 (17) mg]. The recovery time after intracarotid infusion [102 (30) s] was significantly shorter than that after the i.v. infusion [368 (106) s] \( P<0.01 \).

The MAP decreased during the i.v. infusion compared with the pre-anaesthesia period. However, no significant change in MAP was observed after the intracarotid infusion. The MAP at each corresponding time point during intracarotid infusion processes were higher than those in i.v. infusion \( P<0.01 \) (Fig. 1), whereas the plasma propofol concentrations at the same time points were lower during the intracarotid infusion than that the corresponding time point of i.v. infusion \( P<0.01 \) (Fig. 2).

<table>
<thead>
<tr>
<th>Physiological variables</th>
<th>Pre-infusion I</th>
<th>IP</th>
<th>Pre-infusion II</th>
<th>IP+ hyperperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats min(^{-1}))</td>
<td>116 (19)</td>
<td>103 (17)</td>
<td>114 (17)</td>
<td>79 (23)</td>
</tr>
<tr>
<td>( T ) ((^{\circ})C)</td>
<td>37.1 (0.2)</td>
<td>37.1 (0.2)</td>
<td>37.1 (0.1)</td>
<td>37.1 (0.1)</td>
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<tr>
<td>( E)(_)co(_2) (mm Hg)</td>
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<td>40 (1)</td>
<td>38 (1)</td>
<td>38 (1)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>84 (12)</td>
<td>81 (9)</td>
<td>81 (9)</td>
<td>61 (7)</td>
</tr>
<tr>
<td>ICAF (ml min(^{-1}))</td>
<td>117 (24)</td>
<td>108 (19)</td>
<td>113 (16)</td>
<td>132 (22)</td>
</tr>
</tbody>
</table>

Table 1 The physiological variables and ICA flow during intracarotid propofol infusion [\( n=8, s (s) \), \( E\)\(\_\)co\(_2\), end-tidal carbon oxide pressure; HR, heart rates; IP, intracarotid propofol infusion; ICAF, internal carotid artery blood flow; MAP, mean arterial pressure; Pre-infusion I, state before intracarotid propofol infusion; Pre-infusion II, state before intracarotid propofol infusion under cerebral hyperperfusion condition. *\( P<0.01 \) vs Pre-infusion II; \( P<0.01 \) vs IP.
Intracarotid propofol infusion did not induce an obvious decrease in MAP, superior to i.v. administration. The dose requirement during intracarotid propofol infusion was lower than that for i.v. administration and the time required for recovery was shorter after intracarotid infusion than that after i.v. infusion. An increase in CBF increased the dose requirement for intracarotid propofol infusion. Our study demonstrates that intracarotid infusion of propofol is haemodynamically safe. No systemic hypotension occurred during and after the propofol infusion.

The chemical structure of propofol is 2,6-di-isopropyl phenol. Previous work shows that a mixture with an oil solution of propofol and saline at ratios of 1:1, 1:2, 1:4, and 1:10 shows no remarkable change in quality under room temperature up to 2 h, which indicates the physicochemical stability of the diluted solution. We believe that the diluted propofol used for the Wada test at a mixture ratio in the above-mentioned range would not differ from the propofol 1% in essence.

It is known that one of the major side-effects of i.v. propofol infusion is hypotension. The result of Experiment 1 in this study also showed that MAP decreased significantly during i.v. propofol infusion. However, no decrease was observed after intracarotid administration. Smaller dose and lower plasma concentration in the latter may partly account for the unchanged MAP.

It be noted that although most adverse effects observed in the Wada test using propofol were minor, some severe rare ones like increased tone with twitching and rhythmic movements carried the risk of incompletion or inaccuracy of the Wada test. An age older than 55 and a total injection dose >20 mg were regarded as the important risk factors. A systemic review of studies demonstrated that this excitation phenomenon was correlated with a sudden increase in the cerebral concentrations of propofol, without a seizure history. Unlike bolus injection, constant infusion would not result in a similar high peak of propofol concentration, and therefore could reduce the risk of excitation. In addition, propofol infusion provides the possibility to individualize the drug dose during the Wada test. It is possible that once the target anaesthesia depth is reached, the constant infusion would be changed to intermittent infusion to maintain the status. In the Wada test, the significant clinical or electrophysiological changes could be set as the indicators for propofol administration. That means the drug would be targeted and an extended period of hemi-anaesthesia for the Wada test could be provided.

Cerebral perfusion abnormalities are sometimes encountered in patients with refractory epilepsy or aneurysm. To study the effect of CBF increase on intracarotid propofol infusion, we used nicardipine to dilate the blood vessels experimentally. Pharmacologically, nicardipine selectively dilates cerebral and coronary arteries which would change the CBF and help to prevent ischaemia in the brain or the heart. In this study, we found that nicardipine administration augmented the blood flow of ICA by 17%, similar to the results reported by others. With an increased CBF, a larger dose of propofol was required, accompanied by a slower onset time and more rapid recovery. During an intracarotid infusion, the uptake of the drug is a process of drug extraction by both the brain and the CBF. The higher the CBF, the higher the dilution of the drug, the shorter the transit time, and the more rapid the washout. Therefore, an increase of CBF adversely affects the quantity requirement of the intracarotid anaesthetics by decreasing the uptake and enhancing redistribution of the drug from the brain. The same reason accounts for the slower onset time and more rapid recovery during intracarotid propofol infusion with cerebral hyperperfusion challenge. This indicates that the dose requirement of propofol for the Wada test may be increased in patients with a cerebral hyperperfusion state.

Some studies have indicated that the AAI is affected by CBF; however, others claim that alteration of AAI is not significant if the decrease of CBF is no more than 40%. In our opinion, only a large decrease in CBF can alter the anaesthetic depth, when it is large enough to jeopardize the supply/demand balance in O2. This level was not achieved in our study since CBF was only moderately increased by nicardipine.

In summary, our study provides an experimental basis for propofol in application of intracarotid infusion in the Wada test. Our data suggest that intracarotid infusion of propofol may offer the advantage for the Wada test to reduce excitation risk, individualize the dosage, and easily handle the anaesthetic time during test. Our data also indicate that patients with cerebral hyperperfusion state may need a larger dose of anaesthetics in the Wada test.

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