Thiopental bolus during carotid endarterectomy–rational drug therapy?

J.A. Moffat PH D, M.J. McDougall BSC, D. Brunet MD, F. Saunders MD, E.S. Shelley MD, F.W. Cervenko MD, B. Milne MD

Ten studies were performed to examine the time course of arterial and venous thiopental concentrations following the administration of thiopental (4 mg·kg^{-1} over 3 min) for cerebral protection during carotid occlusion in nine patients undergoing elective carotid endarterectomy; in five patients the time course of EEG change was also studied. The arterial and venous thiopental concentrations were similar with no evidence of a sustained arterial–venous gradient. The average arterial concentration was 20.1 μg·ml^{-1} ± 10 (SD) at 2 min after thiopental, and fell rapidly to 13.0 μg·ml^{-1} ± 3.2 at 5 min, 10.7 μg·ml^{-1} ± 4.4 at 10 min and 6.2 μg·ml^{-1} at 30 min. After thiopental the EEG record showed an increase in delta activity and in four patients a burst suppression pattern was seen. The duration of burst suppression activity was variable (130 to 367 seconds) but in all instances cortical activity had returned to the pre-thiopental level by five to ten minutes. Thus concentrations of thiopental of 10–30 μg·ml^{-1} were associated with EEG burst suppression and both were seen only within the first five minutes after drug administration. In contrast the carotid artery was occluded for considerably longer (26 ± 4) minutes.

We conclude that, since there was no sustained arterial–venous gradient, either arterial or venous concentrations are adequate for the study of thiopental pharmacokinetics. However, using burst suppression as an index of cerebral protection with thiopental it appears that the administration of thiopental (4 mg·kg^{-1} over three minutes) before carotid occlusion is not adequate to protect for the duration of the carotid endarterectomy procedure.

Key words

SURGERY: carotid endarterectomy; ANAESTHETICS, INTRAVENOUS: thiopental; barbiturate protection.

Over the last 25 years, revascularization procedures have been performed on an increasing number of patients with evidence of extracranial vascular occlusive disease. While the primary aim of carotid endarterectomy is the prevention of stroke, this operation itself may induce a transient or permanent neurologic deficit. Precipitating factors for stroke during the perioperative period include carotid artery thrombosis, emboli, reperfusion injury, and cerebral injury during carotid occlusion, and estimates of stroke frequency range from one to ten per cent.[1–5]

Since induced ischaemia may occur, several procedures have been advocated to protect the brain during the period of carotid occlusion. Although the optimal therapy remains controversial, the methods used include insertion of an internal carotid shunt,[1] the use of vasopressors to elevate systemic blood pressure[6] and the use of barbiturates as protective agents.[7]

The clinical use of barbiturates for cerebral protection is based on extensive experimental evidence in animal models of induced cerebral ischaemia and on anecdotal clinical information; neither the efficacy of these drugs nor the dose or concentration required has been established in prospective clinical trials.[8] However, the experimental evidence has been convincing and the clinical studies have been encouraging. In one such clinical study, EEG

From the Departments of Anaesthesia, Medicine and Surgery, Queen's University, Kingston, Ontario.

Supported by a grant from Associated Medical Services.

Address correspondence to: Dr. Brian Milne, Department of Anaesthesia, Queen's University, Kingston, Ontario, K7L 3N6.

monitoring was used both as an assessment of function and as an endpoint of drug therapy. Thiopental was titrated to produce a 15–30 second EEG burst suppression during the period of carotid occlusion in seven patients who were at risk of an intraoperative ischaemic event as evidenced by EEG slowing during a trial period of carotid occlusion. With the use of thiopental no neurologic sequellae resulted following carotid occlusion. Although this population was small, the report suggested that the barbiturates had provided some protection when given by this method.[7]

Titration to produce the EEG change (15–30 sec burst suppression) required the administration of repeated boluses of thiopental to a total dose of approximately 3 gm.[7] At present, in most centres where barbiturates are used during carotid endarterectomy, the drug is given only once as a 4–5 $mg \cdot kg^{-1}$ bolus prior to application of the clamp.[9] The objective of the current study was to administer thiopental (4 $mg \cdot kg^{-1}$) prior to carotid clamping and document the time course of (1) EEG changes and (2) arterial and venous concentrations, in an attempt to assess this method of drug therapy. Since an arterial-venous (A-V) gradient has been shown for other lipophilic drugs[10] both arterial and venous samples were analysed to examine whether an A-V gradient exists for thiopental.

Methods

Ten studies were performed in nine male patients with an average age of 59.7 years (range 41–71) and weight of 89 kg (range 72–100). All patients were of ASA Physical Status III and presented for surgery with angiographically documented lesions of the carotid artery. Two of the patients had had a previous completed stroke, seven were hypertensive and six of these were receiving antihypertensive therapy including diuretics, beta-adrenergic blocking agents and alpha-methyldopa. Seven patients were receiving acetylsalicylic acid therapy as prophylaxis against a further ischaemic event. All patients were scheduled for elective carotid endarterectomy and gave informed consent to participate in the research study.

Three patients received diazepam (10 or 15 mg) prior to surgery while all others received no premedication. A 20 gauge cannula was placed in a radial artery for blood pressure recording and blood sampling, and a central venous line was inserted via an antecubital vein for venous sampling. Control arterial and venous blood samples (3 ml) were withdrawn and anaesthesia was induced with intravenous thiopental (4 $mg \cdot kg^{-1}$ over 3 min). Following administration of succinylcholine the trachea was intubated, and anaesthesia was maintained with nitrous oxide, oxygen (FIO_2 = 0.33) enflurane, pancuronium, fentanyl and controlled ventilation.

In five of the studies eight gold cup electrodes were placed according to the International 10–20 system and the electroencephalograph (EEG) was recorded continuously on a Grass Model 8 recorder, until removal of the carotid artery clamp. The carotid artery was exposed in a standard fashion and the area was infiltrated with lidocaine. Before carotid occlusion intravenous phenylephrine was titrated to elevate systemic blood pressure to approximately 20 per cent above resting level and thiopental (4 $mg \cdot kg^{-1}$ over 3 min) was given. The clamp was applied and the surgery completed in the standard manner; the average time for carotid artery occlusion was 26 min ± 4 (SD) (range 18–30 min).

Both arterial and venous blood samples (3 ml) were withdrawn into tubes containing no anticoagulant for determination of thiopental concentrations at the following times: 0, 2, 5, 10, 20, 30, and 45 minutes after induction. The control sample for the second thiopental dose was withdrawn just before drug administration and subsequently at 2, 5, 10, 20, 30, 45, and 60 min, and at 2, 4, 6, 9, 12 and 24 hours. All samples were refrigerated for at least 30 minutes, centrifuged, and the serum was decanted and frozen at −20° C.

Sample analysis

Serum samples were extracted with hexanes using m-dinitrobenzene (DNB) as the internal standard. The hexanes supernatant was evaporated to dryness at room temperature under a stream of dry nitrogen gas and the residue in each tube was dissolved in benzene. A standard curve was prepared in serum from normal volunteers by the addition of DNB and thiopental to produce final concentrations of 1 $\mu g \cdot ml^{-1}$ and 0–20 $\mu g \cdot ml^{-1}$ respectively. The samples were chromatographed using a Hewlett packard 5711A gas–liquid chromatograph with a nitrogen–phosphorus selective detector. This method was sensitive to 0.5 $\mu g \cdot ml^{-1}$ which gave a peak to noise

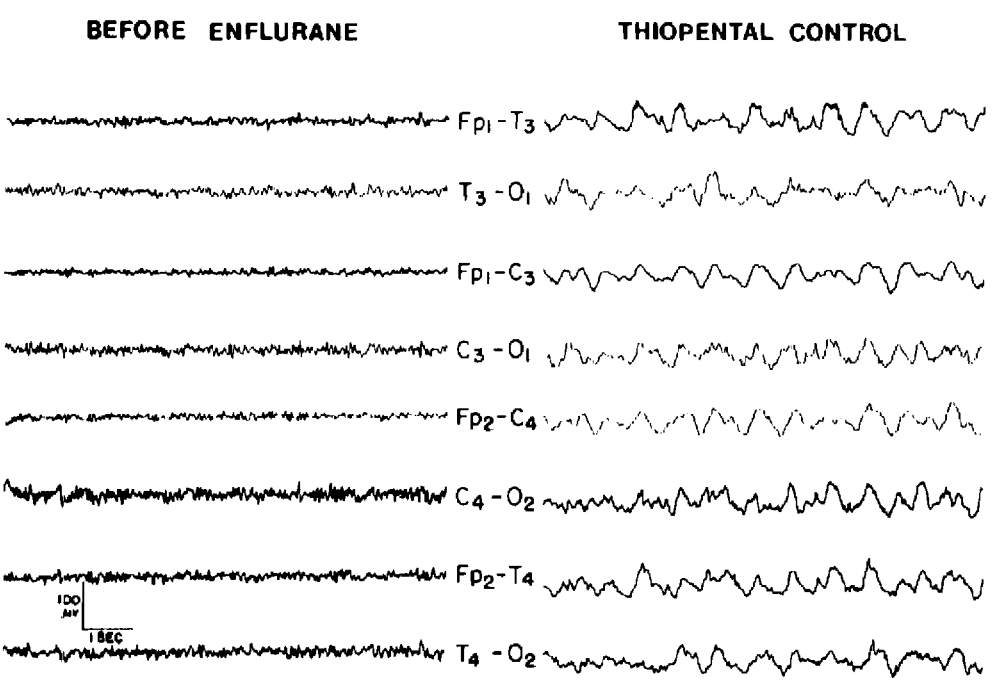

FIGURE 1 Representative tracing from one patient (MH) showing EEG baseline β activity before enflurane. The addition of enflurane resulted in slower activity during the control period before the administration of thiopental and occlusion of the carotid artery.

ratio of greater than three; the recovery of thiopental was 79 per cent with a coefficient of variation of five per cent at 20 $\mu g \cdot ml^{-1}$.*

Results

The EEG record obtained from one patient is shown in Figures 1 and 2. The patient had had a previous completed stroke and the baseline activity recorded from the left hemisphere showed a lower amplitude than that recorded from the right hemisphere. Under anaesthesia the EEG tracing (Fig. 1) showed predominantly beta with some theta activity and the administration of enflurane resulted in an increase in delta activity. Following the administration of thiopental delta activity became more prominent and there was some burst suppression. The suppression pattern shown in Figure 2 occurred at two minutes after thiopental and was associated with arterial and venous concentrations of 28.4 $\mu g \cdot ml^{-1}$ and 32.3 $\mu g \cdot ml^{-1}$ respectively. At five minutes, with an arterial concentration of 13.9 $\mu g \cdot ml^{-1}$ there was no burst suppression (Fig. 2) and by ten minutes the EEG had returned to the pre-anaesthetic pattern.

The EEG was recorded in five patients. With the administration of the thiopental bolus before clamping there was an increase in delta activity in all patients and in four of the patients a burst suppres-

*Pure thiopental, which was used as a chromatography standard, was obtained from Nucro Technics Limited, Scarborough, Ontario. m-Dinitrobenzene (Grade V) was obtained from Sigma Chemical Co., St. Louis, Mo. Benzene (pesticide grade) and hexanes (spectroanalyzed) were obtained from Fisher Scientific Limited, Ottawa, Ontario, and all chromatography supplies were obtained from Chromatographic Specialties, Brockville, Ontario.

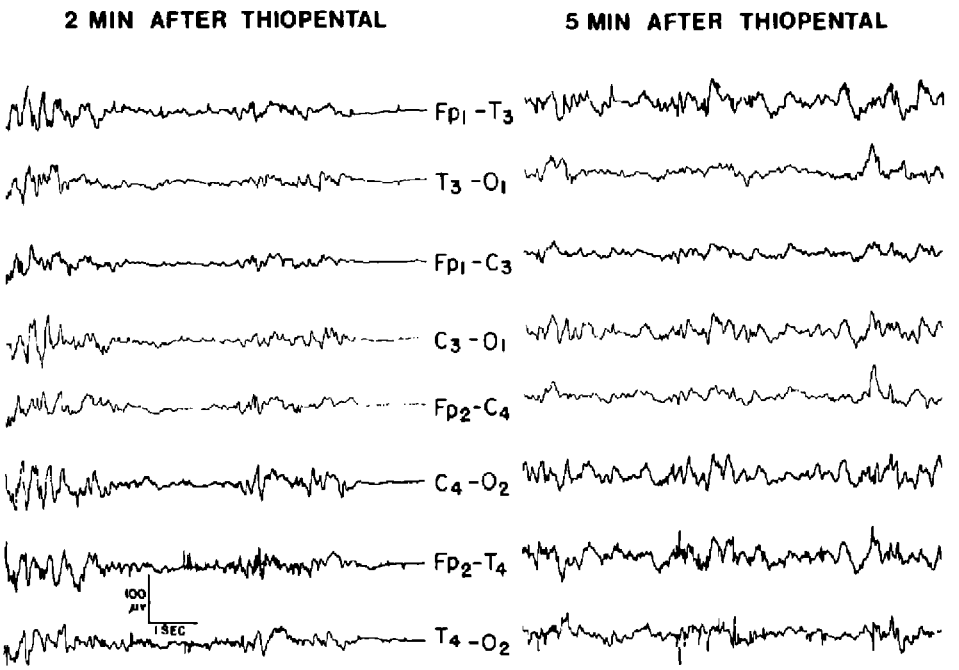

FIGURE 2 Burst suppression pattern seen in one patient (MH) 2 min following thiopental (4 $mg \cdot kg^{-1}$ over 3 min). Thiopental concentrations were 28.4 $\mu g \cdot ml^{-1}$ (arterial) and 32.4 $\mu g \cdot ml^{-1}$ (venous) at this time. At five minutes, with thiopental concentrations of 13.9 $\mu g \cdot ml^{-1}$ (arterial) and 18.0 $\mu g \cdot ml^{-1}$ (venous) burst suppression was no longer apparent.

sion pattern was observed. In all instances where burst suppression was seen this pattern was evident by the end of the three minute period of thiopental administration; however, the longest period of suppression (range 13–40 seconds) and duration of burst suppression activity (range 130–367 seconds) varied between patients. In all patients the cortical activity had returned to the pre-thiopental level by 5–10 minutes after the end of the thiopental administration.

The arterial thiopental concentrations achieved during the surgical period are shown in Figure 3. The thiopental concentration reached 10.0 $\mu g \cdot ml^{-1}$ ± 5.1 at 5 min and was reduced to 5 $\mu g \cdot ml^{-1}$ ± 3.6 at 30 min. The second bolus, given when the carotid artery had been prepared for clamping, was administered at 55.5 min ± 8.6 after the first dose; at this time the arterial thiopental concentration was 2.6 $\mu g \cdot ml^{-1}$ ± 1.5. As seen in Figure 3 the concentrations achieved were slightly greater following the second bolus compared to the first and the differences reached statistical significance at the 10, 20, and 45 minute points ($p \leq 0.05$, Student's paired t test). Half lives were calculated from regression lines fitted to a log linear plot of the arterial concentrations in each patient from 120 min to 24 hr following the second bolus; the average $t_{\frac{1}{2}}$ was 7.8 hr ± 4.9.

Simultaneous arterial and venous samples were obtained in seven patients and the results during the carotid clamp period are shown in Figure 4. At 2 min following the second infusion the average arterial and venous concentrations were 24.4 $\mu g \cdot ml^{-1}$ ± 8.7 and 26.5 $\mu g \cdot ml^{-1}$ ± 11.1 respectively; the concentrations fell rapidly to 7.4 $\mu g \cdot ml^{-1}$ ± 2.1 and 7.5 $\mu g \cdot ml^{-1}$ ± 3.4 respectively by 30 min and were not statistically different at any time ($p > 0.05$, Student's paired t test).

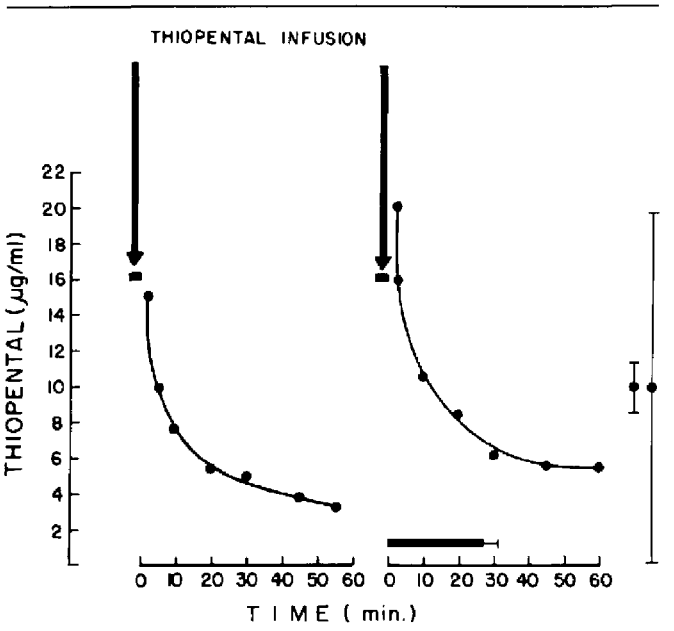

FIGURE 3 Arterial thiopental concentration following administration of thiopental (4 $\mu g \cdot kg^{-1}$ over 3 min) during induction and before occlusion of the carotid artery. The time between thiopental doses was 55.5 min ± 8.6 (SD). The duration of carotid occlusion (26 min ± 4) is indicated. All data are averages and smallest and largest standard deviations are indicated.

Discussion

This study shows that a thiopental bolus given before carotid clamping results in transient changes in the EEG which are characterized by an increase in delta activity and periods of burst suppression. These changes occurred during the 3 min period of drug administration, were evident at 2 min and had disappeared by 5 to 10 min following thiopental dosing. The EEG effects were associated with high arterial and venous concentrations of thiopental (10–30 $\mu g \cdot ml^{-1}$) and the disappearance of the EEG effects paralleled the rapid fall in thiopental concentrations. There was no evidence of residual barbiturate effects on the EEG at the time of removal of the carotid clamp.

The optimal anaesthetic and surgical management of the carotid endarterectomy patient remains controversial. Complicating any assessment of the benefit of therapy, e.g., barbiturates or the use of shunts, is the uncertain etiology of stroke and the unknown incidence of cerebral anoxia during the procedure. In a recent retrospective study in 345 patients undergoing elective carotid endarterectomy under regional anaesthesia, Steed *et al.* (1982) found an overall incidence of stroke due to cerebral anoxia of only 0.3 per cent, while the incidence due to thromboembolic reperfusion phenomena or hypotension was much higher (5.8 per cent).[5] Since barbiturate protection would only be of benefit in instances of cerebral anoxia, if these statistics are representative a very large prospective study would be required to show an improvement in outcome. Although the incidence of stroke due to anoxia appears small, the morbidity associated with stroke is devastating to the individual.[8] In those patients with bilateral carotid disease or an incomplete Circle of Willis who are at greater risk of an ischaemic event, a therapeutic regimen with a protective agent such as thiopental could be beneficial.

The mechanism for barbiturate protection is unclear; the use of barbiturates for protection is

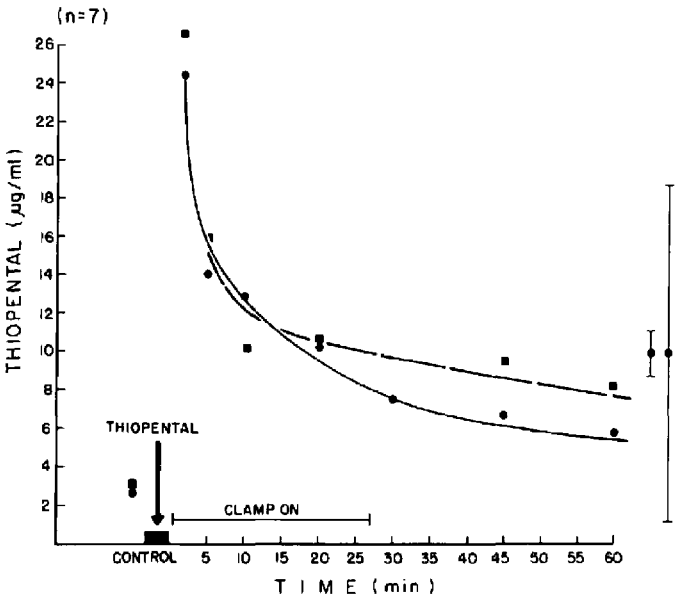

FIGURE 4 Arterial and venous thiopental concentrations in seven patients following thiopental (4 mg·kg^{-1} over 3 min) before carotid occlusion. Control arterial (●) and venous (■) concentrations were 3.3 μg·ml^{-1} ± 6 (SD) and 4.2 μg·ml^{-1} ± 2.5 respectively. Duration of carotid occlusion is indicated. All data are averages and smallest and largest standard deviations are shown.

based on studies in laboratory animals and on limited retrospective clinical studies. In the experimental animal, barbiturates have been shown to protect the brain when given before or shortly after induced focal ischaemia in dogs,[11,12] and baboons.[13] However, in these studies large barbiturate doses (20–120 mg·kg^{-1}) were used and were associated with sustained high blood concentrations (12–40 μg·ml^{-1}).[13] Clinically, in seven carotid endarterectomy patients, Gross *et al.* (1981),[7] titrated the administration of repeated boluses of thiopental to produce 15–30 second burst suppression for the total period of carotid clamping. These patients were selected from a population of 41 as those deemed to be at risk since abnormal EEG tracings were obtained during a trial period of carotid clamping. None of these patients suffered a neurologic deficit. Although not measured, based on the current study it is likely that thiopental concentrations were maintained in the 10–30 μg·ml^{-1} range to achieve this EEG effect.

It is unlikely that the regimen used in the current study provides cerebral protection. As shown here, the concentrations of thiopental following the second bolus peaked and waned rapidly, as was expected from the known lipophilicity and rapid distribution of the drug. Associated with the rapid fall in concentration, the EEG effects also disappeared rapidly. Using EEG burst suppression as an index of a protective concentration,[14] benefit could only be expected for less than the first five minutes while the carotid artery was occluded for almost 30 minutes.

The basis for the use of the 4 mg·kg^{-1} bolus is unclear, although its use has been reported in several institutions.[9] This dose has not been explored in clinical trials, and the only experimental study using a 4 mg·kg^{-1} dose was an early study of

Yatsu *et al.* (1972) which showed protection against global ischaemia in four rabbits using $4\,mg \cdot kg^{-1}$ methohexital.[15] Thus the research basis for this therapy appears to originate from a study in a small group of rabbits with global instead of focal ischaemia, and treated with a different drug (i.e., methohexital rather than thiopental).

The concentrations of thiopental achieved in blood were slightly higher after the second bolus than during induction. As anticipated, the drug initially was rapidly distributed but measurable concentrations persisted for 24 hours. A $t_{\frac{1}{2}}$ of 7.8 hr ± 4.9 was determined, a value intermediate between values of 5.1 and 12.0 hr which are reported in the literature.[15,16]

No arterial-venous gradient was seen following the administration of thiopental. This observation is of interest since both arterial and venous measurements have been used in studies of thiopental kinetics.[18] A gradient was anticipated since a difference has been shown between arterial and venous concentrations of other lipophilic drugs including nitroglycerin and alcohol[10,19] during infusion, although these gradients reversed following infusion. Further study is required to determine whether an arterial-venous gradient exists for thiopental during infusion. However, it appears that either arterial or venous measurements suffice for pharmacokinetic analysis of thiopental in the post-infusion stage.

In summary, this study shows that the administration of a thiopental bolus results in a brief elevation in concentrations and transient EEG burst suppression. Thus, using burst suppression as a therapeutic index of cerebral protection, bolus therapy is inadequate to protect for the duration of carotid occlusion during carotid endarterectomy. From a pharmacokinetic standpoint a thiopental infusion titrated to achieve the desired EEG effect may be a logical approach. However, hypotension and other undesirable cardiac effects could complicate the administration of a high barbiturate load. Further study is required to determine whether barbiturates protect the brain during carotid endarterectomy and, if so, to establish the optimal therapeutic regimen for their use.

Acknowledgements

The authors would like to thank the nurses of the Operating Room, Recovery Room and Neurological Intensive Care Unit and the EEG technicians at the Kingston General Hospital for their assistance.

References

1 *Baker WH, Dorner DB, Barnes RW.* Carotid endarterectomy: Is an indwelling shunt necessary? Surgery 1977; 82: 321–6.

2 *Collins GJ, Rich NM, Andersen CA, McDonald PT.* Stroke associated with carotid endarterectomy. Am J Surg 1978; 135: 221–5.

3 *Stanford JR, Lubow M, Vasko JS.* Prevention of stroke by carotid endarterectomy. Surgery 1978; 83: 259–63.

4 *Sundt TM Jr, Sharbrough FW, Piepgras DG, Kearns TP, Messick JM Jr, O'Fallon WM.* Correlation of cerebral blood flow and electroencephalographic changes during carotid endarterectomy. Mayo Clinic Proc 1981; 56: 533–43.

5 *Steed DL, Peitzman AB, Grundy BL, Webster MW.* Causes of stroke in carotid endarterectomy. Surgery 1982; 92: 634–41.

6 *Boysen G, Engell HC, Henriksen H.* The effect of induced hypertension on internal carotid artery pressure and regional cerebral blood flow during temporary carotid clamping for endarterectomy. Neurology 1972; 22: 1133–44.

7 *Gross CE, Adams HP Jr, Sokoll MD, Yamada T.* Use of anticoagulants, electroencephalographic monitoring, and barbiturate cerebral protection in carotid endarterectomy. Neurosurgery 1981; 9: 1–5.

8 *Yatsu FM.* Pharmacologic protection against ischemic brain damage: need for prospective human studies. Stroke 1982; 13: 745 (Editorial).

9 *Wade JG.* Carotid endarterectomy: The anesthetic challenge. American Society of Anesthesiologists Refresher Course Lectures 1977; #218.

10 *Armstrong PW, Moffat JA, Marks GS.* Arterial-venous nitroglycerin gradient during intravenous infusion in man. Circulation 1982; 66: 1273–6.

11 *Corkill G, Chikovani OK, McLeish I, McDonald LW, Youmans JR.* Timing of pentobarbital administration for brain protection in experimental stroke. Surg Neurol 1976; 5: 147–9.

12 *Yonas H, Dujovny M, Nelson D et al.* The controlled delivery of thiopental and delayed cerebral revascularization. Surg Neurol 1981; 15: 27–34.

13 *Hoff JT, Smith AL, Hankinson HL, Nielsen SL.* Barbiturate protection from cerebral infarction in primates. Stroke 1975; 6: 28–33.

14 *Bruce DA, Gennarelli TA, Langfitt TW.* Resuscita-

tion from coma due to head injury. Crit Care Med 1978; 6: 254–69.

15 *Yatsu FM, Diamond I, Graziano C, Lindquist P.* Experimental brain ischemia: protection from irreversible damage with rapid-acting barbiturate (Methohexital). Stroke 1972; 3: 726–32.

16 *Ghoneim MM, Van Hamme MJ.* Pharmacokinetics of thiopentone: effects of enflurane and nitrous oxide anaesthesia and surgery. Br J Anaesth 1978; 50: 1237–42.

17 *Burch PG, Stanski DR.* The role of metabolism and protein binding in thiopental anesthesia. Anesthesiology 1983; 58: 146–52.

18 *Jung D, Mayersohn M, Perrier D, Calkins J, Saunders R.* Thiopental disposition as a function of age in female patients undergoing surgery. Anesthesiology 1982; 56: 263–8.

19 *Wilkinson PK, Rheingold JL.* Arterial-venous blood alcohol concentration gradients. J Pharmacokin Biopharm 1981; 9: 279–307.

Résumé

On a étudié à dix occasions chez neuf patients l'évolution des concentrations artérielles et veineuses de thiopental après son administration à une dose de 4 $mg \cdot kg^{-1}$ donnée en trois minutes. Cette dose était donnée comme protection cérébrale pendant l'occlusion de la carotide lors d'endartérectomie carotidienne. Chez cinq patients on a également étudié l'évolution de l'EEG. Les concentrations artérielles et veineuses de thiopental étaient similaires et il n'y eut pas lieu de penser qu'il existe un gradient artério-veineux. La moyenne des concentrations artérielles était de 20.1 ± 10 (DS) $\mu g \cdot ml^{-1}$ deux minutes après l'injection et diminuait rapidement à 13.0 ± 3.2 $\mu g \cdot ml^{-1}$ à cinq minutes, 10.7 ± 4.4 $\mu g \cdot ml^{-1}$ à dix minutes et à 6.2 $\mu g \cdot ml^{-1}$ à 30 minutes. Après le thiopental, l'EEG a montré une augmentation de l'activité delta et chez quatre patients une suppression des bouffées. La durée de la suppression des bouffées était variable (130 à 367 secondes) mais dans tous les cas l'activité corticale était revenue à son niveau pré-thiopental après cinq à dix minutes. Des concentrations de thiopental de 10 à 30 $\mu g \cdot ml^{-1}$ ont été associées avec la suppression des bouffées, conditions qui ne furent réalisées que dans les cinq minutes après l'administration du thiopental. Par contre la durée de l'occlusion de la carotide était beaucoup plus longue (26 ± 4 minutes).

Nous concluons que, comme il n'y a pas de gradient artério-veineux, les mesures de la concentration artérielle ou veineuse sont adéquates pour l'étude de la pharmacocinétique du thiopental. Cependant, si on utilise la suppression des bouffées à l'EEG comme un index de protection cérébrale avec le thiopental, il semble que la dose de 4 $mg \cdot kg^{-1}$ donnée en trois minutes avant l'occlusion de la carotide n'est pas adéquate pour toute la durée de l'endartérectomie.