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Barbiturates for Cerebral Aneurysm Surgery

A Review of Preliminary Results

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Summary

Ninety-two cerebral aneurysm cases treated by clipping under moderate hypothermia are reviewed. Twenty-three of these cases received pentobarbitone during surgery in doses sufficient to render the EEG flat. The overall combined mortality and morbidity (complication rate) among 69 non-barbiturate cases was 21.7%. There were significant differences in results between aneurysms in different anatomical locations. The complication rate among eight middle cerebral artery aneurysm cases was 62.5% and among ten internal carotid artery bifurcation cases 40%, while that among nineteen internal carotid artery cases was 16% and among 27 anterior communicating complex cases 7.4%. The overall complication rate among 23 pentobarbitone cases was 17%. There were no complications among eight middle cerebral artery cases; one of two internal carotid bifurcation cases became hemiplegic following occlusion of the middle cerebral artery at its origin. The complication rate among nine internal carotid cases was 22%. No difficulties were experienced regarding haemodynamic stability or cardiac rhythm while using pentobarbitone at normothermia or at 28 °C. It is suggested that cerebral aneurysms involving the middle cerebral artery which appear to be most at risk may have the most to gain by the prophylactic use of pentobarbitone during surgery.

Introduction

Cerebral vasospasm and the potentially catastrophic consequences of cerebral ischaemia and oedema which may ensue remain a real threat to the cerebral aneurysm patient and to the neurosurgeon today. Barbiturates have been shown to be effective in primate stroke models both in reducing the extent of cerebral infarction observed histologically[12,21,4,36] and in ameliorating the neurological sequelae to permanent arterial occlusion[29,19,20] as well as in focal ischaemia of limited duration[26]. It is much less clear at the present time how much protection barbiturates can offer in global ischaemia, simulating the cardiac arrest situation[9,5,30,32,33].

Much of the published clinical trials of barbiturates to date are concerned with the control of intractable intracranial hypertension in head injuries[28,24,17] metabolic encephalopathy[16,34] or in cerebral oedema of other aetiologies[35] rather than with brain protection in acute, focal cerebral ischaemia. The difficulty of assessing the results of barbiturate therapy in the case of head injury patients is increased further by the inevitably wide variation in several important factors. These include the site, nature and extent of the brain injury; the time interval from the injury to the institution of therapy, which may be too long to allow maximum benefit from barbiturates[5,7,27]; the adequacy of respiratory and haemodynamic support during this interval and the extent of development of secondary changes in that time.

Planned cerebral aneurysm surgery offers a much more controlled situation for the assessment of the efficacy of barbiturates in combating the effects of cerebral ischaemia, although cases still vary in some respects and the ischaemic risk to each cannot usually be precisely estimated. Nevertheless, the patient's clinical and neurological state immediately prior to surgery is accurately known; the nature of the pathology and of the intervention are precisely known with the aid of peroperative angiography and it is possible to administer barbiturates without delay when required.

Although barbiturates may be effective when given within a limited time after the onset of an ischaemic insult[5,7,27] we have chosen to load the patients prophylactically and to discontinue administration when the period of greatest hazard is estimated to be over. In the event of complications such as permanent vascular occlusion or severe, persistent segmental vasospasm the

administration of barbiturates can be continued into the postoperative period without interruption. Our experience so far with this technique has enabled us to reappraise the indications for the use of barbiturates in high doses in cerebral aneurysm surgery.

Patients and Methods

During the period 1974 to 1983 one hundred and twenty cerebral aneurysm cases were treated operatively in the Neurosurgical Department of the University Hospital in Groningen. In the latter four years twenty-eight cases were given prophylactic pentobarbitone in high doses during surgery. The first 50 non-barbiturate cases were consecutive and were studied retrospectively from existing records. Barbiturates were initially used after two cases at this time developed serious complications. Six patients who received thiopentone sodium are not presented here since this technique is no longer used[3]. The first 19 pentobarbitone cases were consecutive; the next six were selected according to availability of staff and facilities and the estimated risk to the patient of the additional postoperative period of immobility, rather than according to the preoperative Hunt and Hess grade[14] or the anatomical location of the aneurysm. The last three pentobarbitone cases were selected according to our findings reported here, *i.e.*, according to the anatomical location of the aneurysm.

All aneurysms had ruptured at least once prior to surgery. Surgery was carried out as soon after admission as the patients' neurological condition was stable but was usually postponed in the presence of marked cerebral vasospasm. Cerebral angiography (Seldinger technique) was performed immediately before surgery in nearly all cases, under local anaesthesia whenever possible, to assess the state of the vessels; the catheter was left in place for peroperative angiography to allow confirmation of the position of the clip and the patency of vessels and to assess the severity and extent of vasospasm after clipping, if present. Surgery was performed by one operator (JWFB) in all except five nonbarbiturate cases and in all but four pentobarbitone cases (three clipped cases). A frontal approach was used with magnification. Self-retaining retraction was not employed. In all cases except one, surgery was performed under moderate hypothermia at 27 to 29 °C. This was induced by surface cooling with cold water following premedication with a lytic cocktail (pethidine, 50 mg; promethazine, 25 mg; chlorpromazine, 25–50 mg and atropine, 0.5 mg, intramuscularly). The waterbath serves as an operating table with a 15° head up tilt. Surgical access was further improved by the lumbar drainage of up to 120 ml of cerebrospinal fluid via a hatch in the watherbath after the dura was open.

All patients received dexamethasone, 16 mg daily, starting 24 hours preoperatively. The dose was reduced from the third postoperative day in non-barbiturate cases and the fifth postoperative day in pentobarbitone cases.

Anaesthesia

Anaesthesia was given or supervised by one of the authors (M. B.) in all except one non-barbiturate case. Anaesthesia was induced with thiopentone sodium in all non-barbiturate cases. Etomidate was used in the pentobarbitone cases in order to minimize the development of tolerance as far as possible before giving pentobarbitone[1, 31]. Intubation was carried out with the aid of suxamethonium chloride and anaesthesia was continued with pethidine, pancuronium and ventilation with 33% oxygen, 65% nitrous oxide and 2% carbon dioxide to maintain the arterial carbon dioxide tension at 4 to 5 kP at the prevailing body temperature. Sodium nitroprusside was used when necessary to control the arterial blood pressure and to reduce it to a mean of 50 to 70 mm Hg during dissection of the aneurysm. Inspired gases were humidified at 38 °C in all the pentobarbitone cases and in the last 30 non-barbiturate cases. All patients were rewarmed to 36.5 °C at the end of surgery. Non-barbiturate cases were generally awake at the end of surgery and were extubated in the absence of complications. Frontal epidural pressure was monitored postoperatively in the first 52 non-barbiturate cases and in all the pentobarbitone cases.

The patient and relatives were informed in advance when pentobarbitone was used. A bolus of 600 mg was given during cooling and a 1% infusion at 5 to 10 mg/minute started at the same time. Cerebral activity was monitored using a Cerebral Function Monitor (CFM) (Devices)[18]. A signal obtained from biparietal scalp electrodes is subjected to heavy filtering and logarithmic amplitude compression, retaining only frequencies between 2 and 15 Hz. It is displayed as a single trace and can be recorded continuously on a chart recorder for long periods of time. A typical CFM trace during loading with pentobarbitone is shown in Fig. 1. The rate of

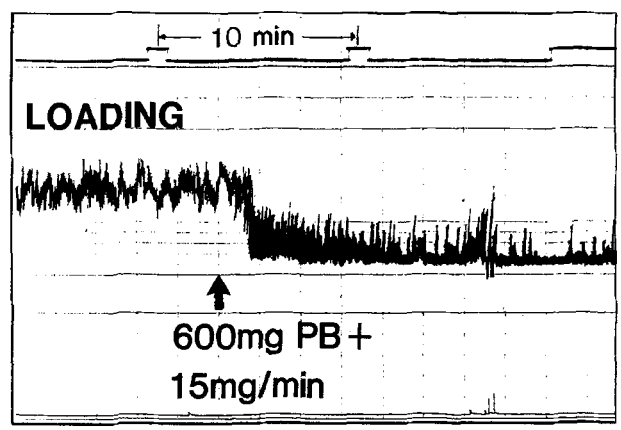

Fig. 1. Cerebral function monitor recording during loading with pentobarbitone

pentobarbitone infusion is adjusted to keep the CFM trace flat until the clip has been placed and checked by angiography. Pentobarbitone is then discontinued. The total amount of pentobarbitone given is therefore related to the duration of the procedure.

Postoperatively, patients who had received pentobarbitone were ventilated for as long as necessary. They were extubated after a mean of 37 hours postoperatively. Postoperative monitoring included epidural intracranial pressure, CFM, end-tidal CO_2 and intermittent arterial blood gas, acid-base and electrolyte estimation.

Intraoperative monitoring included: EKG; arterial blood pressure via a radial cannula (Statham transducers); end-tidal CO_2 (Godart Mark II capnograph); oesophageal, nasopharyngeal and skin temperatures (Ellab); right atrial pressure; CFM; intermittent arterial blood gas, acid-base and electrolyte estimation and urine production.

Non-barbiturate patients received phenytoin sodium, 300–500 mg, during rewarming. Pentobarbitone cases were started on phenytoin, 300 mg daily, 24–36 hours postoperatively.

Sodium pentobarbitone was obtained from the Hospital Pharmacy. Pentobarbitone levels were estimated using high performance liquid chromatography.

Focal neurological deficits only are reported in this study.

Results

1. Haemodynamic Aspects

Systemic arterial blood pressure and the incidence of cardiac dysrhythmias were similar when using pentobarbitone to those seen in non-barbiturate cases at comparable temperatures. Hypotension was never seen. Sodium nitroprusside was frequently required during the administration of pentobarbitone to control the arterial blood pressure during dissection of the aneurysm, particularly in the presence of cerebral vasospasm.

2. Pentobarbitone

The total dose of pentobarbitone given varied between 1.4 and 4.0 g or 19–57 mg/kg, with a mean of 2.25 g or 34.2 mg/kg. Serum levels of pentobarbitone

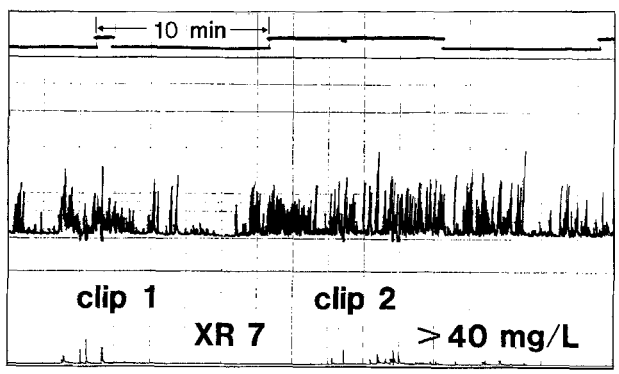

Fig. 2. Cerebral function monitor recording during dissection of aneurysm. Pentobarbitone infusion 5 mg/min; patient temperature 28—29 °C. Serum pentobarbitone level greater than 40 mg/l

during clipping of the aneurysm varied between 15 and 55 mg/l with a mean of 31 mg/l. The CFM trace was flat in all but two cases, which showed a burst-suppression pattern. There was no consistent relationship between serum levels and activity seen on the CFM trace. A response to surgical retraction on the CFM trace persisted in all cases at all times (Fig. 2).

3. (i) Non-Barbiturate Group—Neurological Results

The overall immediate postoperative combined mortality and morbidity or complication rate in the 86 non-barbiturate cases was 22.2%. In order to eliminate from these results the contribution made by recurrent haemorrhage in cases where no clip could be placed, we shall confine our attention throughout this report to cases where a clip was placed. In the 69 non-barbiturate cases where a clip was placed the complication rate was 21.7% (Table 1). About three quarters of the cases were

Table 1. *Overall Results in 69 Clipped Non-Barbiturate Cases*

Dead	3	21.7%
Permanent new deficit	12	
Transient deficit	2	78%
Uncomplicated	52	

clinically uncomplicated postoperatively. Cases so classified do not include those with a transient new neurological deficit. An isolated new third nerve paresis following internal carotid artery (ICA) aneurysm surgery is not counted here as a new neurological deficit.

Table 2 shows a breakdown of the 69 clipped non-barbiturate cases with respect to the anatomical location of the aneurysms. Anterior communicating artery (ACoA) cases here include aneurysms of the A_1A_2 junction as well as those arising from the anterior communicating artery itself. Anterior cerebral artery (ACA) here denotes aneurysms of the distal ACA; ICA denotes those aneurysms arising at the level of the posterior communicating artery and ICA-bif. denotes,

Table 2*. *Results in 69 Non-Barbiturate Cases with Respect to Anatomical Location of Aneurysm*

	MCA	ICA-bif	ICA	ACoA	ACA	Total
Dead	1	1	1	0	0	3
ND	4	3	2	2	1	12
TD	1	1	0	0	0	2
U	2	5	16	25	4	52
%U	25	50	84	92.5	80	75.4
Total	8	10	19	27	5	69

* ND denotes a permanent new focal neurological deficit; TD denotes a transient neurological deficit; U denotes a total absence of clinical complications; other abbreviations see text.

aneurysms at the bifurcation of the internal carotid artery into the anterior and middle cerebral arteries. Among eight cases where the aneurysm was situated at the bi- or trifurcation of the middle cerebral artery (MCA) there was one death and four permanent new neurological deficits, a complication rate of 62.5%. Two cases ran a clinically uncomplicated course. Among ten ICA-bifurcation cases there was one death and three new deficits, a complication rate of 40%; fifty percent of cases were clinically uncomplicated

postoperatively. Of nineteen ICA cases 84% were totally uncomplicated and among 27 ACoA cases 92.5% were uncomplicated with a complication rate of 7.4%. There were only five aneurysms of the distal ACA; one developed a permanent new neurological deficit.

3. (ii) Pentobarbitone Cases—Neurological Results

The overall results for 23 pentobarbitone cases where a clip was placed are shown in Table 3. The overall combined mortality and morbidity was 17%.

Table 3. *Overall Results in 23 Clipped Pentobarbitone Cases*

Dead	2	17%
Permanent new neurological deficit	2	
Transient deficit	3	83%
Uncomplicated	16	

Table 4*. *Results in 23 Barbiturate Cases with Respect to Anatomical Location of Aneurysm*

	MCA	ICA-bif	ICA	ACoA	ACA	Total
Dead	0	0	1	1	0	2
ND	0	1	1	0	0	2
TD	2	1	0	0	0	3
U	6	0	7	1	2	16
%U	75	0	78	50	100	69.5

* Abbreviations—see Table 2.

These results are broken down with respect to location of the aneurysms in Table 4. The greatest difference between the pentobarbitone and non-barbiturate results appears in cases involving the MCA. The complication rate among eight non-barbiturate MCA cases was 62.5% as compared to zero among eight pentobarbitone MCA cases. This is significant according to Fisher's exact probability test, $p = 0.0265$. There were only two pentobarbitone ICA-bifurcation cases, of which one developed a permanent new neurological deficit related to occlusion of the middle cerebral artery at its origin following intraoperative rupture of the aneurysm; the other had a transient deficit. Among nine ICA cases the complication rate was 22%.

4. Preoperative State

Fifteen non-barbiturate cases were in Hunt and Hess' grade III or IV[14] preoperatively, of which eight or 53% either died or sustained a new neurological deficit in the immediate postoperative period. Among the MCA and ICA-bifurcation cases, five were in grade III or IV preoperatively, of which all developed a new deficit or died. Six out of nine non-barbiturate ICA, ACoA and ACA cases in grade III or IV preoperatively had no permanent postoperative sequelae.

In the pentobarbitone group three MCA cases were in Hunt and Hess' grade III or IV preoperatively without developing any deficit postoperatively.

The difference between the outcomes in non-barbiturate and pentobarbitone MCA cases in preoperative Hunt and Hess' grade III or IV is significant according to Fisher's exact probability test, $p = 0.046$.

5. Interval from Subarachnoid Haemorrhage to Surgery

The interval from the last subarachnoid haemorrhage to surgery was longer than 14 days in all the non-barbiturate MCA cases. One non-barbiturate ICA-bifurcation case had a two day interval and developed a permanent new deficit postoperatively. All pentobarbitone cases involving the MCA had an interval of 18 days or more. One pentobarbitone ICA case with a two day interval and with severe, global cerebral vasospasm died (see below).

6. Mortality and Morbidity

(i) Non-barbiturate group: 15 cases: Occlusion of the distal ACA following rupture of an ACA aneurysm resulted in a permanent new hemiparesis in one case; in one ACoA case occlusion of an ACA at its origin was followed by massive cerebral oedema and ultimately by

Table 5*. *Results of Cases Involving the Middle Cerebral Artery*

	No barbiturates			Pentobarbitone	
	MCA		ICA-bif	MCA	ICA-bif
Total	8		10	8	2
Dead	1	62.5%	1	0	0
ND	4		3	0	1
TD	1		1	2	1
U	2		5	6	0
%U	25		50	75	0

* Abbreviations—see Table 2.

a residual neurological deficit. Severe vasospasm unrelated to aneurysm rupture was seen in one case and in seven cases the aneurysm ruptured intraoperatively. In some of these marked vasospasm was recorded after the clip was placed. Three cases had been in Hunt and Hess' grade III or IV preoperatively but had no other recognizable factors predisposing them to risk. One ICA-bifurcation case was one week postpartum and thus probably in a hypercoagulable state, on account of which hypothermia was not used (no angiograms are available for this case). One ACoA case had no attributes of note except for a different surgeon.

(ii) Pentobarbitone group: 4 cases: All four complications in this group followed intraoperative rupture of the aneurysm. One death occurred in an ICA case who was soporose (Hunt and Hess' grade IV) with severe, global cerebral vasospasm preoperatively and where recurrent haemorrhage had taken place two days prior to surgery. The second death was due to massive pulmonary embolism in an ACoA case where both anterior cerebral arteries had been occluded by clips (also other surgeon). One new neurological deficit was the result of occlusion of the MCA at its origin following intraoperative rupture in an ICA-bifurcation case; the last had a delayed onset (ICA case without peroperative angiography).

7. *Cerebral Vasospasm and Its Consequences*

The overall incidence of angiographically documented vasospasm during surgery not associated with intraoperative aneurysm rupture was $^{4}/_{50}$ in the non-barbiturate group and $^{3}/_{18}$ in the pentobarbitone group (Table 6).

The sequelae to vasospasm in the non-barbiturate group as a whole, regardless of whether or not this was associated with intraoperative aneurysm rupture, and assuming that rupture is invariably followed by a degree of vasospasm, include three deaths, seven permanent new neurological deficits and two transient deficits, a combined mortality and morbidity of $^{10}/_{23} = 43\%$. If thirteen cases where intraoperative rupture occurred without explicit documentation of vasospasm are excluded, then it is seen that six out of the ten remaining cases either died or developed a permanent deficit.

In the pentobarbitone group one case with severe, global vasospasm died and in one ICA case who developed a new deficit following intraoperative rupture no angiography was performed. There were no permanent sequelae to marked segmental vasospasm in five cases, following rupture in two cases and in the absence of rupture in three cases. A complication rate following vasospasm with or without rupture of 10 out of 23 non-barbiturate cases thus compares with 2 out of seven pentobarbitone cases.

Considering now cases involving the middle cerebral artery separately, *i.e.*, MCA and ICA-bifurcation cases (Table 7), vasospasm in the absence of aneurysm rupture was recorded in three out of eight non-barbiturate cases and in one out of seven pentobarbitone cases. Intraoperative rupture occurred in ten non-barbiturate cases of which five either died or developed a permanent new deficit. When these ten cases are assumed to have had a degree of vasospasm following rupture, the incidence of permanent sequelae to vasospasm among non-barbiturate cases is seen to be $^{7}/_{13}$ or 54%. This compares with four cases of rupture or vasospasm in the pentobarbitone group, of which one

Table 6. *Incidence and Sequelae of Vasospasm**

No barbiturates (69):	4 vasospasm, no rupture	2 ND
	6 rupture + vasospasm	2 dead, 2 ND, 1 TD
	13 rupture "alone"	1 dead, 3 ND, 1 TD
Pentobarbitone (23):	3 Vasospasm, no rupture	1 TD
	3 rupture + vasospasm	1 dead, 2 TD
	1 rupture "alone"	1 ND

* Abbreviations—see Table 2.

Table 7*. *Incidence and Sequelae of Vasospasm in Cases Involving MCA*

Non-barbiturate	No rupture	Rupture
8 MCA	4: 3 vasospasm/2 ND	4: 1 ND, 1 dead
10 ICA-bif	4: nil	6: 2 ND, 1 dead
Pentobarbitone	**No rupture**	**Rupture**
8 MCA	7: 1 vasospasm + TD	1: vasospasm + TD
2 ICA-bif	0	2: 1 vasospasm + TD, 1 ND (vascular occlusion)

* Abbreviations—see Table 2.

developed a new deficit; this was related to vascular occlusion and not to vasospasm (see above). It is thus possible that the incidence of vasospasm not associated with intraoperative aneurysm rupture and of the sequelae to vasospasm may be lower in the pentobarbitone MCA and ICA-bifurcation cases than in non-barbiturate cases. However, the number of pentobarbitone cases is at present too small for the difference between the two groups to reach statistical significance.

8. *General Clinical Observations*

The quality of recovery in pentobarbitone cases was generally excellent. Many patients were able to go home seven to ten days postoperatively in spite of having spent the first day or two on a ventilator. One ICA case developed severe cerebral oedema during emergence from pentobarbitone but subsequently recovered uneventfully following a second administration of pentobarbitone. In one case occlusion of a branch of the MCA resulted in no clinically recognizable neurological deficit, although a CT scan four days postoperatively showed cerebral oedema with a marked midline shift (Fig. 3). In another ICA case severe spasm of the distal ICA and of at least the A_1 segment of the ACA followed clipping of the aneurysm so that the ACA was not visible after rewarming (Fig. 4). The patient made an uneventful recovery.

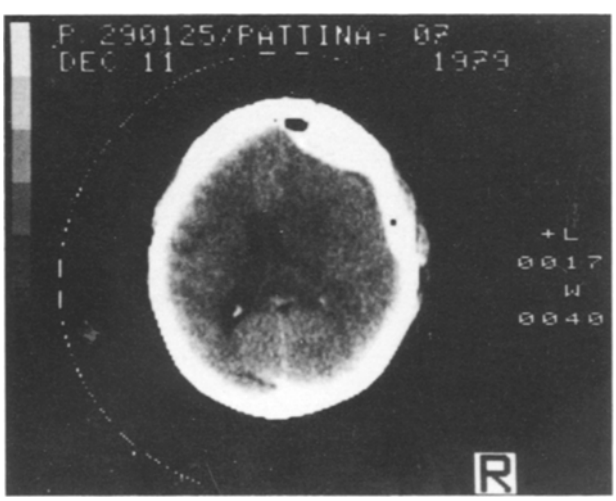

Fig. 3. Computer tomography scan 4 days postoperatively in a pentobarbitone loaded MCA case where an MCA branch was occluded during surgery. No clinical manifestations

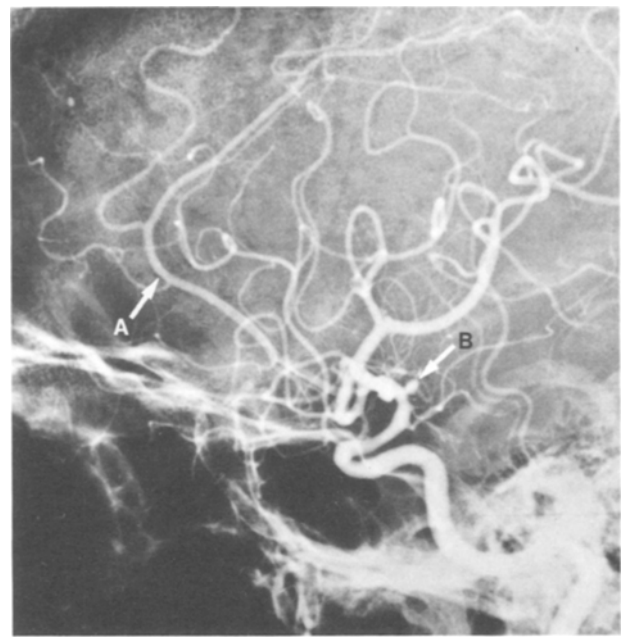

Fig. 4 a. Peroperative angiogram performed on the day of operation in a pentobarbitone loaded ICA case. Anterior cerebral artery—*A*; aneurysm—*B*

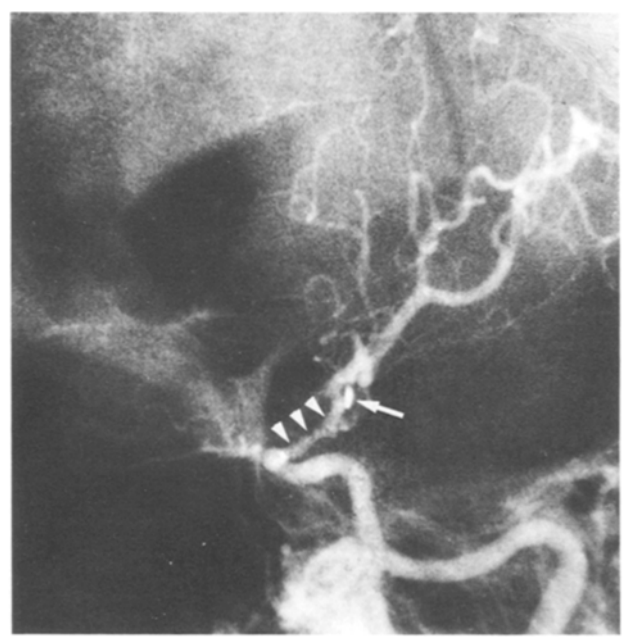

Fig. 4 b. Peroperative angiogram after clipping and rewarming in the same case, showing clip (arrow) and severely spastic distal ICA (arrow-heads). ACA is not visible

Non-neurological complications in three cases may be at least partly attributed to the use of barbiturates with a prolonged period of postoperative immobility: one patient died as the result of massive pulmonary embolism, another developed a deep vein thrombosis two weeks postoperatively and there was one case of pulmonary infection which delayed the patient's extubation for more than 24 hours.

Discussion

The poor results in the non-barbiturate MCA cases contrast with those of non-barbiturate ACoA cases. Poor results for MCA aneurysms are reported by a number of authors including Krayenbühl[15], Nornes and Wikeby[22] Rasmussen *et al.*[23] and Artiola *et al.*[2], but not by others including Hugosson[13], Saito *et al.*[25] and Gonski *et al.*[10]. Differences in surgical technique, patient selection and management may account for the variation in these results.

Although there is little difference in outcome between clipped cases in the pentobarbitone and non-barbiturate groups overall, a significant difference is seen when MCA cases are considered separately. Here, a complication rate (or combined mortality and morbidity) of 62.5% in the non-barbiturate cases compares with zero in the pentobarbitone cases. This difference is significant according to Fisher's exact probability test, $p = 0.0256$. Since there are only two ICA-bifurcation cases in the pentobarbitone group they cannot be considered alone; when ICA-bifurcation cases are considered together with MCA cases (as cases involving the middle cerebral artery) a complication rate of 50% in the non-barbiturate group compares with 10% in the pentobarbitone group ($p = 0.08$). Moreover, this 10% represents a case of arterial occlusion by a clip.

The difference in results between non-barbiturate and pentobarbitone MCA cases is not readily accounted for by a difference in the proportion of high risk cases in the two groups, that is, in preoperative Hunt and Hess' grades III and IV cases, nor by the number of cases with a short haemorrhage-to-surgery interval. A systematic difference between the two groups which cannot be eliminated is that the pentobarbitone cases were ventilated for 16 to 46 hours postoperatively while the non-barbiturate cases were not. Immobilisation and ventilation at normocarbia were found by Bleyaert *et al.*[6] to be beneficial in primates following an episode of global ischaemia. It remains uncertain to what extent this difference could have contributed to our results.

Because the MCA supplies the pre- and postcentral gyri and Broca's area, ischaemia and infarction in its territory produce limb weakness, hemiparesis or dysphasia. These focal deficits are well defined and easy to identify and are therefore more likely to be accurately and reliably recorded than, for instance, a psychological change. This is particularly true when cases are considered retrospectively. The high incidence of complications among the non-barbiturate MCA cases will also tend to highlight any improvement accompanying the use of barbiturates. Considering MCA cases alone further reduces the inhomogeneity among cases, although their numbers are much reduced. Simple conventional statistical tests do not take this into account.

The ACA also contributes to the arterial supply of the motor cortex pertaining to the leg. The small number of distal ACA aneurysms in this study does not allow assessment of the possible benefits of pentobarbitone therapy in these cases.

Our results are consistent with the experimental work of Selman *et al.*[26] who observed no amelioration of the effects of permanent occlusion of the MCA at its origin in the baboon by barbiturates. They are also broadly comparable with those of Hoff *et al.*[11] who gave pentobarbitone during aneurysm surgery with hypothermia in four cases of permanent and three cases of temporary arterial occlusion. Three of the four cases with permanent occlusion developed neurological deficits while a temporary occlusion of 90 minutes duration did not result in a deficit. We have seen no apparent beneficial effect of barbiturates in the presence of severe, global vasospasm. As experimental studies have led us to expect, pentobarbitone appears to be effective in incomplete, focal ischaemia where some flow either remains or is maintained via a collateral supply or where the ischaemia is of limited duration.

Hoff *et al.*[1] and Corkill *et al.*[36] describe a protective effect of barbiturates which is dose related. It is perhaps only a matter of curiosity to note in this context that all the pentobarbitone cases in our study who developed serious postoperative complications had peak serum pentobarbitone levels of less than 25 mg/l, while the case with severe spasm of the ACA which recovered uneventfully had a peak level of around 50 mg/l. In the case where an MCA branch was occluded without clinical sequelae the peak serum pentobarbitone level was 29 mg/l and in the four cases who had transient deficits the peak level ranged from 29 to 40 mg/l.

The figures for the incidence of cerebral vasospasm in our cases cannot be regarded as reliable for a number of reasons. A much slowed blood flow associated with cerebrovascular constriction is common at 27° to 29 °C. In a number of cases severe segmental vasospasm seen at these temperatures immediately after clipping was subsequently seen to resolve on rewarming to 35 °C. Vasospasm should thus strictly be considered to be present only if its persists after rewarming. However, angiography was not repeated in all cases after rewarming when vasospasm was recorded at hypothermic temperatures nor was it repeated

postoperatively. On the other hand, vasospasm may develop postoperatively after a delay, perhaps following intraoperative aneurysm rupture or manipulation, while not evident immediately after clipping. In a few cases angiograms were not available and in some ICA cases no angiography was performed. These considerations may explain in part why the difference in the incidence and sequelae of vasospasm between the non-barbiturate and pentobarbitone groups is not as clear as the difference between the outcomes. Vasospasm presumably is responsible for cerebral ischaemia which produces a large proportion of the complications of aneurysm surgery. We are, however, satisfied that the risk of developing vasospasm is not increased by the use of pentobarbitone together with moderate hypothermia.

Psychological assessments were made in a number of patients both pre- and postoperatively but were not sufficiently standardized or systematic to allow presentation here. Preoperative assessment is complicated by the enforcement of bed rest and the frequent need for sedation and postoperative assessment by the effects of frontal lobe retraction which the frontal approach entails. However, our observation of the generally excellent quality of recovery usually seen in pentobarbitone cases leads us to speculate that careful and systematic psychological testing might reveal better results in the pentobarbitone-loaded ACoA and ACA cases than in non-barbiturate cases.

The anaesthetic technique we have described in this paper involves little added risk to the patient when adequate monitoring is employed and is no more troublesome during surgery than conventional techniques. Our results suggest any added risk to the patient and extra work load for the medical and nursing personnel in the postoperative period is likely to be justified for aneurysms involving the middle cerebral artery, which appear to be particularly prone to complications and where we have seen a significant improvement using pentobarbitone. It can only be speculated that a comparable improvement may be seen in aneurysms of the distal ACA and that psychological complications might also be shown by suitable testing to be reduced by prophylactic pentobarbitone loading. We feel that our results so far are encouraging and that these aspects deserve further evaluation.

Acknowledgements

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References

1. Altenburg, B. M., Michenfelder, J. D., Theye, R. A., Acute tolerance to thiopentone in canine cerebral oxygen consumption studies. Anesthesiology *31* (1969), 443—448.
2. Artiola i Fortuny, L., Prieo-Valiente, L., Long term prognosis in surgically treated intracranial aneurysms. Part 2: Morbidity. J. Neurosurg. *54* (1981), 35—43.
3. Belopavlovic, M., Buchthal, A., Cerebral function monitoring for assessment of barbiturate therapy under moderate hypothermia in cerebral aneurysm surgery. Acta Anaes Belg. *180* (1980), suppl. 31, 93—100.
4. Black, K. L., Weidler, D. J., Jallad, N. S., Sodeman, T. M., Abrams, G. D., Delayed pentobarbital therapy of acute focal cerebral ischaemia. Stroke *9* (1978), 245—249.
5. Bleyaert, A. L., Nemoto, E. M., Safar, P., Stezoski, S. W., Mickell, J. J., Moossy, J., Rao, G. R., Thiopental amelioration of brain damage after global ischaemia in monkeys. Anesthesiology *49* (1978), 390—398.
6. Bleyaert, A. L., Safar, P., Stezoski, S. W., Nemoto, E. M., Moossy, J., Amelioration of postischaemic brain damage in the monkey by immobilization and controlled ventilation. Crit. Care Med. *6* (1978), 112—113.
7. Corkill, G., Chikovani, O. I., McLeish, I., McDonald, L. W., Youmans, J. R., Timing of pentobarbital administration for brain protection in experimental stroke. Surg. Neurol. *5* (1976), 147—149.
8. Corkill, G., Sivalingham, S., Reitan, J. A., Gilroy, B. A., Helphrey, M. G., Dose dependency of the post-insult protective effect of pentobarbital in the canine experimental stroke model. Stroke *9* (1978), 10—12.
9. Goldstein, A., Wells, B. A., Keats, A. S., Increased tolerance to cerebral anoxia by pentobarbital. Arch. Int. Pharmacodyn. *161* (1966), 138—143.
10. Gonski, A., Gonski, L., Selecki, B. R., Blum, P. W., Matheson, J. M., Intracranial aneurysms. A survey of the results of surgical treatment at the Prince Henry Hospital, Sydney, 1972—1976. Med. J. Austr. *1* (1978), 250—252.
11. Hoff, J. T., Pitts, L. H., Spetzler, R., Wilson, C. B., Barbiturate for protection from cerebral ischemia in aneurysm surgery. In: Cerebral function, metabolism and circulation, p 7.18 (Ingvar, D. M., Lassen, N. A., eds.). Copenhagen: Munskgaard. 1977.
12. Hoff, J. T., Smith, A. L., Hankinson, H. L., Nielsen, S. L., Barbiturate protection from cerebral infaction in primates. Stroke *6* (1975), 28—33.
13. Hugosson, R., Intracranial arterial aneurysms. Considerations on the upper age limit for surgical treatment. Acta Neurochir. (Wien) *28* (1973), 157—164.
14. Hunt, W. E., Hess, R. M., Surgical risk as related to time of intervention in the repair of intracranial aneurysms. J. Neurosurg. *28* (1968), 14—19.
15. Krayenbühl, H. A., Yaşargil, M. G., Flamm, E. S., Tew, J. M., Microsurgical treatment of intracranial saccular aneurysms. J. Neurosurg. *37* (1972), 678—686.
16. Marshall, L. F., Rauscher, A., Kauffman, N. M., Pentobarbital therapy for intracranial hypertension in metabolic coma. Crit. Care Med. *6* (1978), 1—5.

17. Marshall, L. F., Smith, R. W., Shapiro, H. M., The outcome with aggressive treatment in severe head injuries. Part II: Acute and chronic barbiturate administration in the management of head injury. J. Neurosurg. *50* (1979), 26—30.
18. Maynard, D. E., Prior, P. F., Scott, D. F., Device for continuous monitoring of cerebral activity in resuscitated patients. Br. Med. J. *4* (1968), 404—408.
19. Michenfelder, J. D., Milde, J. H., Influence of anesthetics on metabolic, functional and pathological responses to regional cerebral ischemia. Stroke *6* (1974), 405—410.
20. Michenfelder, J. D., Milde, J. H., Sundt, T. M., Cerebral protection by barbiturate anesthesia. Arch. Neurol. *33* (1976), 345—350.
21. Moseley, J. I., Laurent, J. P., Molinari, G. F., Barbiturate attenuation of clinical course and pathologic lesions in a primate stroke model. Neurology *25* (1975), 870—874.
22. Nornes, H., Wikeby, P., Results of microsurgical management of intracranial aneurysms. J. Neurosurg. *51* (1979), 608—614.
23. Rasmussen, P., Busch, H., Haase, J., Hansen, J., Harmsen, A., Knudsen, V., Marcussen, E., Midholm, St., Olsen, R. B., Rosenørn, J., Schmidt, K., Voldby, B., Hansen, L., Intracranial saccular aneurysms. Results of treatment in 851 patients. Acta Neurochir. (Wien) *53* (1980), 1—17.
24. Rockoff, M. A., Marshall, L. F., Shapiro, H. M., High dose barbiturate therapy in humans—a clinical review of 60 patients. Ann. Neurol. *6* (1979), 194—199.
25. Saito, I., Ueda, Y., Sano, K., Significance of vasospasm in the treatment of ruptured intracranial aneurysms. J. Neurosurg. *47* (1977), 412—429.
26. Selman, W. R., Spetzler, R. F., Roessmann, U. R., Rosenblatt, J. I., Crumrine, R. C., Barbiturate-induced coma therapy for focal cerebral ischemia. Effect after temporary and permanent middle cerebral artery occlusion. J. Neurosurg. *55* (1981), 220—226.
27. Selman, W. R., Spetzler, R. F., Roski, R. A., Roessmann, U. R., Crumrine, R. C., Macko, R., Barbiturate coma in focal cerebral ischemia: relationship of protection to timing of therapy. J. Neurosurg. *56* (1982), 685—690.
28. Shapiro, H. M., Wyte, S. L., Leoser, J., Barbiturate augmented hypothermia for reduction of persistent intracranial hypertension. J. Neurosurg. *40* (1974), 90—100.
29. Smith, A. L., Hoff, J. T., Nielsen, S. L., Larson, C. D., Barbiturate protection in acute focal cerebral ischemia. Stroke *5* (1974), 1—7.
30. Snyder, B. D., Ramirez-Lassepas, M., Sukhum, P., Fryd, D., Sungh, J. H., Failure of thiopentone to modify global anoxic injury. Stroke *10* (1979), 135—141.
31. Steen, P. A., Michenfelder, J. D., Barbiturate protection in tolerant and non-tolerant hypoxic mice. Anesthesiology *50* (1979), 404—408.
32. Steen, P. A., Milde, J. H., Michenfelder, J. D., No barbiturate protection in a dog model of complete cerebral ischemia. Ann. Neurol. *5* (1979), 343—349.
33. Todd, M. M., Chadwick, H. S., Shapiro, H. M., Dunlop, B. J., Marshall, L. C., Dueck, R., The neurological effects of thiopental therapy following experimental cardiac arrest in cats. Anesthesiology *57* (1982), 76—86.
34. Venes, J. L., Shaywitz, B. A., Spencer, D. D., Management of severe cerebral edema in metabolic encephalopathy. J. Neurosurg. *48* (1978), 903—915.
35. Woodcock, J., Ropper, A. H., Kennedy, S. K., High dose barbiturates in non-traumatic brain swelling: ICP reduction and effect on outcome. Stroke *13* (1982), 785—787.
36. Yonas, H., Dujovny, M., Nelson, D., Lipton, S. D., Segal, R., Agdeppa, D., Mazel, M., The controlled delivery of thiopental and delayed cerebral revascularization. Surg. Neurol. *15* (1981), 27—34.

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