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Intraarterial Use of Sodium Methohexital for Provocative Testing during Brain Embolotherapy

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PURPOSE AND METHODS: To assess its vascular effects and safety, we used sodium methohexital (Brevital)—an ultrashort-acting barbiturate—as the provocative intraarterial agent in a series of 30 patients with arteriovenous malformations at a 1% concentration and at doses of less than 5 mg per injection. Digital vascular imaging was performed just prior to and just after the injections. RESULTS: No angiographic or clinical evidence of apparent vasospasm occurred in the trial population (66 vascular pedicle injections in 30 patients). When functional tissue was perfused with 1–6 mg of the 1% Brevital solution, evidence of altered neurologic status became immediately apparent, but cleared within 2 minutes in all cases. None of the patients experienced either prolongation of the induced clinical symptoms or seizures to suggest any adverse effects related to either crystallization of the Brevital or the effects of injecting an alkaline solution in the cerebral circulation. CONCLUSION: Though the full effects of methohexitol in the cerebral circulation remain to be elucidated, existing reports suggest it is a safe provocative agent for use prior to embolotherapy for brain arteriovenous malformations.

Index terms: Arteriovenous malformations, embolization; Provocative testing

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Provocative testing is used to detect angiographically obscure arteries that arise from parent arteries supplying vascular malformations of the brain. The high volume and rapid flow of blood in the arteriovenous malformation's (AVM) afferent arteries can make opacification of small branch vessels to normal functional brain difficult even with high resolution digital subtraction angiography. The most frequently used barbiturate for provocative testing, Amobarbital (1–3), has significant drawbacks including relatively short shelf life and prolonged sedative effects. The prolonged hypnotic effect of repeated injections can significantly increase the duration of an embolization procedure. Similarly, if clinical symptoms are elicited, they are relatively slow to clear, lasting 10–15 minutes. Delay related to the sedative effects of such barbiturates can be overcome with the use of an ultrashort-acting barbiturate such as sodium methohexital (Brevital®-sodium methohexital, Eli Lilly and Company, Indianapolis, IN). However, its intraarterial use in the cerebral circulation has been discouraged because of concern over the possibility of drug-induced vasospasm and/or seizure induction. This paper will review the source for such concerns and present clinical data pertaining to the clinical use of Brevital as an agent in provocative testing prior to brain AVM embolotherapy.

Materials and Methods

Brevital is supplied in a powdered, crystalline form in a vial containing 500 mg, then dissolved in 50 mL of sterile water producing a 1% solution (4). It is critical that the sterile water be devoid of any preservative or bacteriostatic agents. Although it has a shelf life of 6 weeks, we prepare the methohexitol solution at the start of each case. We performed 66 pre- and post-Brevital instillation digital arteriograms on 30 patients with large brain AVMs who underwent staged embolotherapeutic procedures. In most cases, only one vascular pedicle was embolized at each setting to avoid thrombosis of the efferent limb of the vascular malformation or normal perfusion pressure break-
Fig. 1. Representing pre- (A) and post- (B) Brevital injection distal middle cerebral arterial branch angiograms. Subselective catheterization of a distal arterial branch afferent to a parietal lobe AVM reveals no evidence of vascular narrowing following intraarterial injections of Brevital. Total dose in this case is 4 mg. The patient experienced no symptoms to preclude embolization. None of the patients developed neurologic deficits following particle embolization in arteries that revealed negative Brevital provocative testing prior to treatment.

through. In most cases, the vascular pedicle included more than one arterial branch requiring embolic treatment.

All patients were prepped and draped under sterile conditions. A vascular catheterization was performed via percutaneous right femoral artery puncture. Selective catheterizations depended upon the needs of the individual study. For AVM embolotherapy, Tracker 18 catheters were placed successively in one or more appropriate afferent feeding arteries. The angiographic and embolotherapeutic catheterization procedures were performed in a standard fashion. Protocol for the instillation of the drug included an initial test dose of 1 mg. If symptoms were elicited, no additional drug was given, and the catheter was repositioned or removed from the artery. If no symptoms were elicited by the initial 1-mg test dose, then provocative testing was performed, usually with an additional 3 mg. The total Brevital dosage depended on the size of the afferent artery and ranged between 1 mg and 6 mg. The catheter was always flushed with heparinized saline before and after each Brevital instillation.

The clinical and neurologic status of all patients was closely monitored for neurologic deficit or seizure activity during and following Brevital infusion by members of both the Neuroradiology, and either the Neurosurgery or Neurology Departments. Any persistence longer than 5 minutes of the induced neurologic deficit was considered clinical evidence of vasospasm. Digital vascular imaging was performed immediately prior to, and at 1 minute after, the Brevital instillation. Both the patient position and the filming devices remained fixed for both the pre- and post-Brevital angiogram, thereby obviating magnification and projectional differences. The angiographic projection selected was always that which best delineated the long axis of the artery being evaluated. Comparisons were made directly from the printed films, and differences were calculated as a percentile change from the baseline (pre-Brevital) angiogram.

Results

Uncomplicated intraarterial use of a 1\% concentration of Brevital in the cerebral circulation (cervical internal carotid artery) has been reported previously (5, 6). Because of our concern over the possibility of drug-induced seizures or vasospasm, however, we desired the lowest possible dose for superselective cerebral catheter placement. As a consequence, the sodium methohexital dosage in our protocol was empirically set at an initial test dose of 1 mg and a provocative dose of 3 mg. The provocative test was used only when no clinical symptomatology was observed after the initial 1-mg dose. In two cases in which equivocal symptoms were produced, additional 3
mg was given to confirm a negative test. In those cases in which the study was considered negative (e.g., symptom producing), only the 1-mg test dose was required to elicit the symptom complex in all but one case. An additional 3-mg provocative dose was required in this instance to confirm the presence of flow to functional brain (e.g., to confirm a positive test). Embolotherapy proceeded only after a negative provocative Brevital test was substantiated. Oversedation of patients delaying the embolic treatment was not observed in any patients. Furthermore, no untoward or unexpected embolotherapeutic effects following particulate embolizations occurred in any patient in whom the final catheter position produced a negative provocative test.

Pre- and post-Brevital digital angiography was performed in all 66 vascular pedicles to assess arterial lumen size and configuration. No evidence of vasospasm (either focal or diffuse) was evident in the afferent circulation to the AVM in any case (Fig. 1). When vessels to normal cerebral substance arising from arteries to an AVM were apparent (three cases), no vasospasm was observed (Fig. 2). There was no evidence of delayed arteriovenous circulation time following Brevital injection, which would suggest either vasospasm or intercurrent embolization by precipitated Brevital. In those patients in whom functional brain was perfused by angiographically occult branches of the arterial feeders of the AVM, no symptoms persisted beyond 2 minutes without complete or nearly complete clearing. In essence, there was no clinical or radiographic evidence of acute vasospasm or intercurrent embolization induced by the intraarterial injection of the 1% concentration of Brevital.

Additionally, five patients in our series had a history of seizures, either as their presenting symptoms or as a longer term seizure disorder. Neither in these five patients nor throughout the remaining study population, was there any evidence of seizure induction during Brevital testing. Electroencephalogram monitoring was used in two patients; no electrical evidence of seizure activity was observed.

**Discussion**

Intraarterial administration of barbiturates has been utilized as a provocative agent to detect the presence of small arteries perfusing functional brain during intracerebral embolotherapy (usually for AVMs). Historically, the barbiturate most commonly used for this purpose has been sodium amobarbital (Amytal). However, this agent has several drawbacks, including a relatively short shelf life (30 minutes following preparation) and a relatively long tissue effect. Prolonged anesthetic effects can potentially delay the embolotherapeutic process. Previous reports have suggested that intraarterial injections of ultrashort-acting barbiturates, principally Thiopentone, can produce severe vasospasm, thrombosis, and tissue necrosis (7-10). As a consequence, other analogous short-acting barbiturates, principally Brevital, have been avoided for intraarterial provocative testing prior to embolotherapy. The source for such concern regarding vasospasm is based on a number of articles, but primarily on an investigation in which varying concentrations of methohexitone (a similar, but not the same drug formulation) were injected in rabbit ear arteries, causing tissue necrosis in some of the animals (11). Review of these reports revealed, however, that such vascular changes occurred only when concentration of the drug exceeded...
5% and occurred most often at a concentration of 10% or above. Vascular necrosis not only occurred at the higher concentration but also required dosages of over 20 mg per injection. None of the animal-model studies reported vaso-spasm at a concentration below 2.5% (11). Studies by Loeschcke et al have noted that methohexitol in a 1% solution did not produce any tissue damage when injected into the central artery of the rabbit ear (12).

Clinical studies also exist supporting the safe use on intraarterial Brevital in the cerebral circulation (5, 13). Wilmore et al reported the satisfactory use of a 1% concentration of Brevital for Wada testing. They observed no prolonged clinical symptoms to suggest any untoward vascular reaction or spasm (5). There is a case report (14) that describes the inadvertent intraarterial injection of 20 mg of methohexitol into an arm vessel; the patient developed tissue necrosis. However, the same patient had injections of other medications (atropine and meperidine) through the same catheter immediately preceding the Brevital instillation. Any of these drugs alone or in combination might be indicated in this instance. No reports exist, to our knowledge, where intraarterial use of Brevital in the intracranial circulation resulted in stroke or other significant complication.

Brevital is alkaline in solution. It is reconstituted with sterile water for instillation purposes, producing a pH of 10.6–11.6, which is similar to the pH of Amytal solutions (9.6–10.4). At doses under 6 mg and at a concentration of 1%, there is not subjective sensation of burning or any other stimulus for the patient. We observed no instances to suggest that Brevital precipitated on contact with blood to cause inadvertent intercurrent embolization. Likewise, we observed no persistent clinical symptoms to suggest brain injury related to the pH of the drug.

An additional concern regarding the use of Brevital has been possible de novo production of seizures. When methohexitol was first introduced, seizures were frequently encountered. However, subsequent evaluation led to fractionation of the original compound, revealing its two isomeric forms and leading to the identification and subsequent elimination of the isomer primarily responsible for the epileptogenic property. In its current formulation, potential seizure induction with methohexitol is limited to patients with psychomotor epilepsy (15). Wilder (13) notes that when Brevital was administered in an artery contralateral to an epileptogenic focus, only slow waves were seen, again demonstrating the absence of seizure induction in the brain that is not prone to seizure. Additionally, a recent study by Kuroiwa et al (16) utilized methohexitol to prevent postischemic CA1 neural injury after global ischemia in a gerbil model. Their study noted that postischemic carotid infusion of methohexitol actually improved neuronal survival, thus raising the possibility that pretreatment with Brevital in the embolic regions may actually be protective.

It is evident that the full effects of intraarterial use of methohexitol in the cerebral circulation are as yet unknown. However, the existing investigative reports both in animal model and in clinical studies suggest that Brevital, at the 1% concentration and low dose, can be used safely as a provocative agent prior to embolotherapy. It has the advantage of being stable chemically throughout the duration of even a prolonged embolo therapeutic procedure. Furthermore, it can detect perfusion of functional brain at dosages insufficient to cause significant patient sedation or prolonged hypnosis. When clinical symptoms are induced, the dysfunction is very transient, lasting less than 2 minutes in nearly every case. And finally, and possibly most importantly, we have detected no untoward vascular effects—no vasospasm, no necrosis, no persistent clinical symptoms—with the intraarterial use of Brevital in superselectively catheterized cerebral arteries.

References