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Potential Toxic Effects of Superselective Injection of Amobarbital Sodium on Microvasculature: A Study in an Animal Model

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PURPOSE: To determine whether microvascular damage occurs from superselective intraarterial injection of amobarbital sodium using the swine endovascular embolization model. **METHODS:** Thirty-four swine underwent percutaneous femoral puncture for superselective catheterization of the proximal artery of the rete. Varying concentrations of amobarbital sodium were prepared (12.5 to 100 mg/mL solution) in either normal saline or sterile water (105 mOsm/L to 1138 mOsm/L) of which one concentration was infused slowly into one ipsilateral rete. Control infusions were also performed. Histopathologic changes were evaluated at 30 minutes and 10 days after infusion, using standard light and electron microscopy techniques. **RESULTS:** Moderate vasospasm occurred only in three swine at 100 mg/mL amobarbital sodium in normal saline. Light microscopy showed no significant histologic changes in the retia at any of the tested concentrations of amobarbital sodium. Electron microscopy showed ultrastructural alterations in the intima only at the higher amobarbital sodium concentrations. **CONCLUSIONS:** Concerns for inducing significant damage to cerebral microvasculature by superselective injection of amobarbital sodium at the usually recommended concentrations and doses are probably not justified.

Index terms: Interventional neuroradiology, models; Interventional neuroradiology, provocative testing; Brain, microvasculature; Brain, effects of drugs on; Drugs, intraarterial injection; Animal studies

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Provocative testing with the intermediate-acting barbiturate amobarbital sodium (Amytal Sodium) after superselective catheterization of intracranial arteries supplying a cerebral arteriovenous malformation (AVM) is a technique frequently used for pharmacologic evaluation of the vascular supply to normal brain adjacent to the AVM. The premise behind this technique is that small nutrient arteries to functional ("eloquent") cortex may be identified by provoking a temporary, pharmacologically induced neurologic deficit. The use of this type of superselective provocative testing has been intended to improve the margin of safety of both endovascular embolization and surgical resection of cerebral AVMs by identifying AVM feeding pedicles that also supply normal functional brain (1–6).

Although this technique has been used by many neurointerventionalists and has been reported to be safe and effective (1–5), complete pharmacologic, physiologic, and pathohistologic studies of the effects of superselective intraarterial injection of amobarbital sodium and other short-duration barbiturates have not been performed (3, 7).

Some clinicians have been concerned that superselective intraarterial injections of amobarbital sodium mixed in a variety of carrier solutions (eg, saline, contrast media) may have significant toxic effects on either normal pial or

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abnormal nidus microvasculature (3, 8). These concerns originate from early reports of ischemia developing from accidental or experimental intraarterial injection of concentrated amobarbital sodium solutions and other barbiturates (9–12) and more recent anecdotal reports of transient (eg, ischemia caused by vasospasm) and permanent complications (eg, neurologic deficits resulting from hemorrhage and infarction) that were possibly attributable to superselective injections of amobarbital sodium (3).

Thus, the purpose of this study was to determine whether microvascular damage occurs from superselective injection of various concentrations and dosages of amobarbital sodium using a swine endovascular embolization model (13–15).

Methods

The experiments were performed in accordance with guidelines for the use of laboratory animal subjects in research by the UCLA Chancellor's Animal Research Committee and the National Institutes of Health. Thirty-four Red Duroc swine were first sedated with intramuscular diazepam (0.5 mg/kg) and ketamine hydrochloride (20 mg/kg). After intubation, general anesthesia was induced and maintained with continuous inhalation of 1% to 1.5% halothane.

Each swine underwent percutaneous femoral puncture by the Seldinger technique in order to place a #6 French vascular sheath. A Tracker 18 microcatheter and Seeker 14 guide wire (Target Therapeutics, Fremont, Calif) were coaxially placed through a tapered #5.5-4.0 French guiding catheter (Cook, Bloomington, Ind) for superselective catheterization of the ascending pharyngeal artery (artery of the rete). Preinfusion angiography (Fig 1) was performed (*a*) to ensure that no injury to the ascending pharyngeal artery occurred, (*b*) to confirm that the microcatheter was positioned distal to the pharyngeal branch of the ascending pharyngeal artery in order to permit more complete delivery of amobarbital sodium into the rete, and (*c*) to determine the appropriate injection rate for filling the ipsilateral rete, because overinjection will result in cross-filling of the contralateral rete.

Varying concentrations of amobarbital sodium were prepared (12.5, 25, 37.5, 50, and 100 mg/mL solution) in either normal saline or sterile water. This produced osmotic concentrations in the range of 105 mOsm/L to 1138 mOsm/L (Table). A total of 2 mL of one amobarbital sodium concentration were slowly injected into one rete at the predetermined rate based on preinjection angiography. This volume produced total dosages of amobarbital sodium delivered to a given rete in the range of 25 to 200 mg. The average duration of injection was 10 seconds.

Tonicity of amobarbital sodium solutions

Concentration, mg/mL	Tonicity in Sterile Water, mOsm/L	Tonicity in Normal Saline, mOsm/L
12.5	101	409
25.0	202	510
37.5	303	611
50.0	404	712
100	808	1138

Infusions at each specific concentration and tonicity of amobarbital sodium were performed in two different animals, except at concentrations of 50 and 100 mg/mL, which were performed in three and four different animals, respectively. In a separate set of control animals, either sterile water or normal saline (four each) was also injected into a single rete after superselective angiography of the retial system was performed. In all cases postinfusion angiography was performed to ensure that no significant change in catheter position occurred, and to evaluate for any potential vasoreactive responses of the ascending pharyngeal and retial arteries to the infusion. Whenever possible, infusions into individual retia were staggered in time in such a way that a single swine could be used to evaluate two predetermined time intervals for the development of histologic changes. The first injection was given 10 days before killing the animal, to evaluate for long-term changes; the second injection was given 30 minutes before killing, to evaluate short-term changes.

In a separate group of swine the above-described protocol was used to evaluate for potential short-term ultrastructural alterations (particularly involving the endothelium) of the retial vasculature by electron microscopy, because it is possible that acute cellular injury to components of a vessel wall may not be detected by standard light microscopy. For this portion of the study retia were infused with amobarbital sodium solution at concentrations of 12.5 (n = 2), 50 (n = 2), and 100 (n = 3) mg/mL in normal saline and 12.5 (n = 1), 50 (n = 2), and 100 (n = 2) mg/mL in sterile water and evaluated in the short term only.

Each rete was harvested from the skull base immediately after death. Samples for light microscopy were fixed in 10% formalin and embedded in paraffin. The retia were then sectioned and stained with hematoxylin and eosin for evaluation with light microscopy. The retia samples studied with electron microscopy were immediately fixed in 2% glutaral, postfixed with 1% osmium tetroxide, dehydrated in graded alcohol, and embedded in epon/araldite. Standard ultrathin sections of these specimens were produced as described elsewere (16). An experienced neuropathologist (H.V.V.), who was blinded to infusion concentrations/tonicities, evaluated both light microscopic and electron microscopic specimens for evidence of microvascular injury.

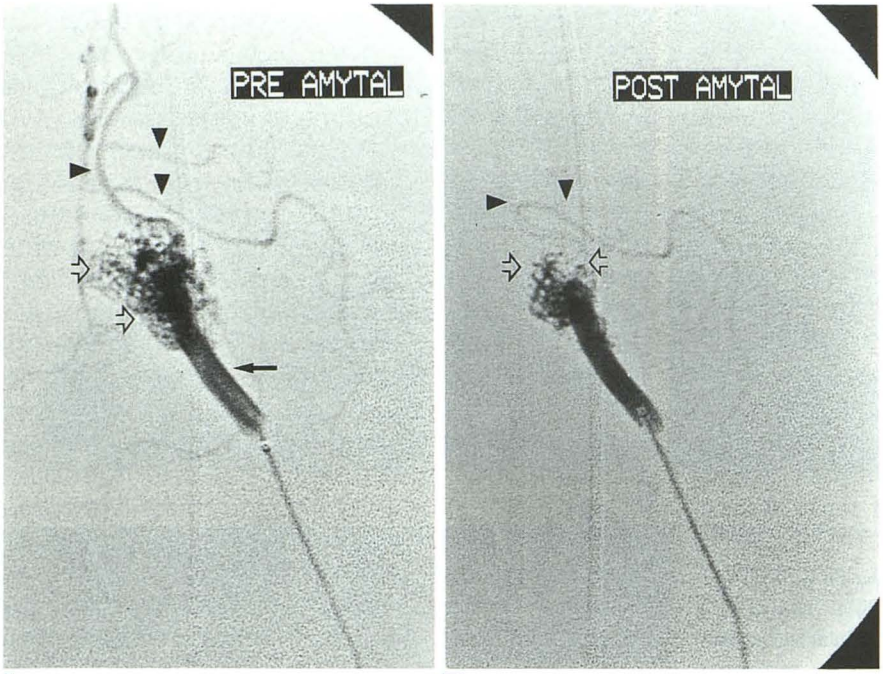

Fig 1. *A*, Preinfusion cerebral angiogram from right ascending pharyngeal injection, anteroposterior projection. There is normal opacification of the ascending pharyngeal artery (*arrow*), rete mirabile (*open arrows*), and intracranial vessels (*arrowheads*).

B, Repeat cerebral angiogram in the same projection 5 minutes after infusion of 100 mg/mL amobarbital sodium dissolved in normal saline shows poor opacification of the rete (*open arrows*) and intracranial vessels (*arrowheads*) caused by moderate ascending pharyngeal and retial vasospasm.

Results

Preinfusion angiography showed no evidence of vasospasm, dissection, or thrombus resulting from superselective catheterization of the ascending pharyngeal artery. Postinfusion angiography was normal at the various amobarbital sodium concentrations, except in three of four swine (75%) infused with 100 mg/mL amobarbital sodium mixed in normal saline (1138 mOsm/L). In these cases, a variable degree of transient moderate to severe vasospasm was observed in the distal ascending pharyngeal artery and retial arteries (Fig 1). The vasospasm also may have extended into the proximal ipsilateral circle of Willis in one case. There were no transient or permanent neurologic deficits observed in these swine upon recovery from general anesthesia. Nearly complete resolution of vasospasm occurred within 15 to 20 minutes in all retia. Repeat superselective angiography 10 days later showed complete resolution of the vasospasm of the ascending pharyngeal artery and no evidence of permanent occlusion of the retial arteries.

Light microscopy showed no significant pathohistologic changes in the retia infused with various concentrations of amobarbital sodium in either the short or long term when compared with controls. Specifically, there was no evidence of angionecrosis, extensive endothelial denuding, intimal encrustation/proliferation, or inflammatory response. Occasional thrombi and one foreign body embolus were seen in 7 of 32 specimens (22%), which had no relationship to the concentration of infused amobarbital sodium. Similar findings of occasional thrombi within saline-infused and sterile water–infused retia (controls) were seen in 3 of 8 specimens (37.5%), indicating that no excessive thromboembolic phenomena occurred in the amobarbital sodium–infused retia (Fig 2).

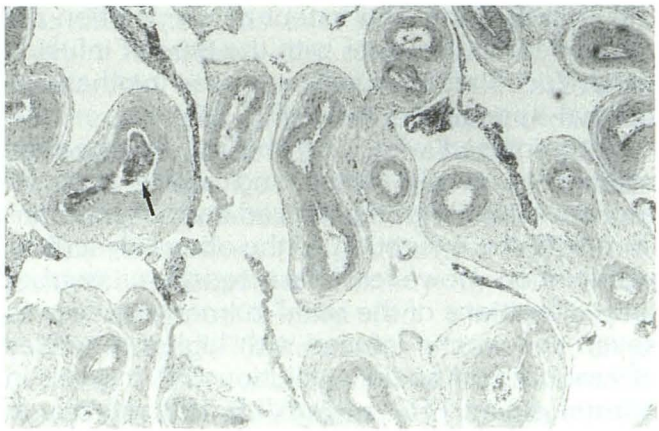

Fig 2. Light microscopy of a control rete mirabile (hematoxylin and eosin; magnification ×10). The retial vessels are muscular microarteries in the size range of 50 to 250 μm. Occasional thromboemboli (*arrow*) were seen in both control and amobarbital sodium–infused retia.

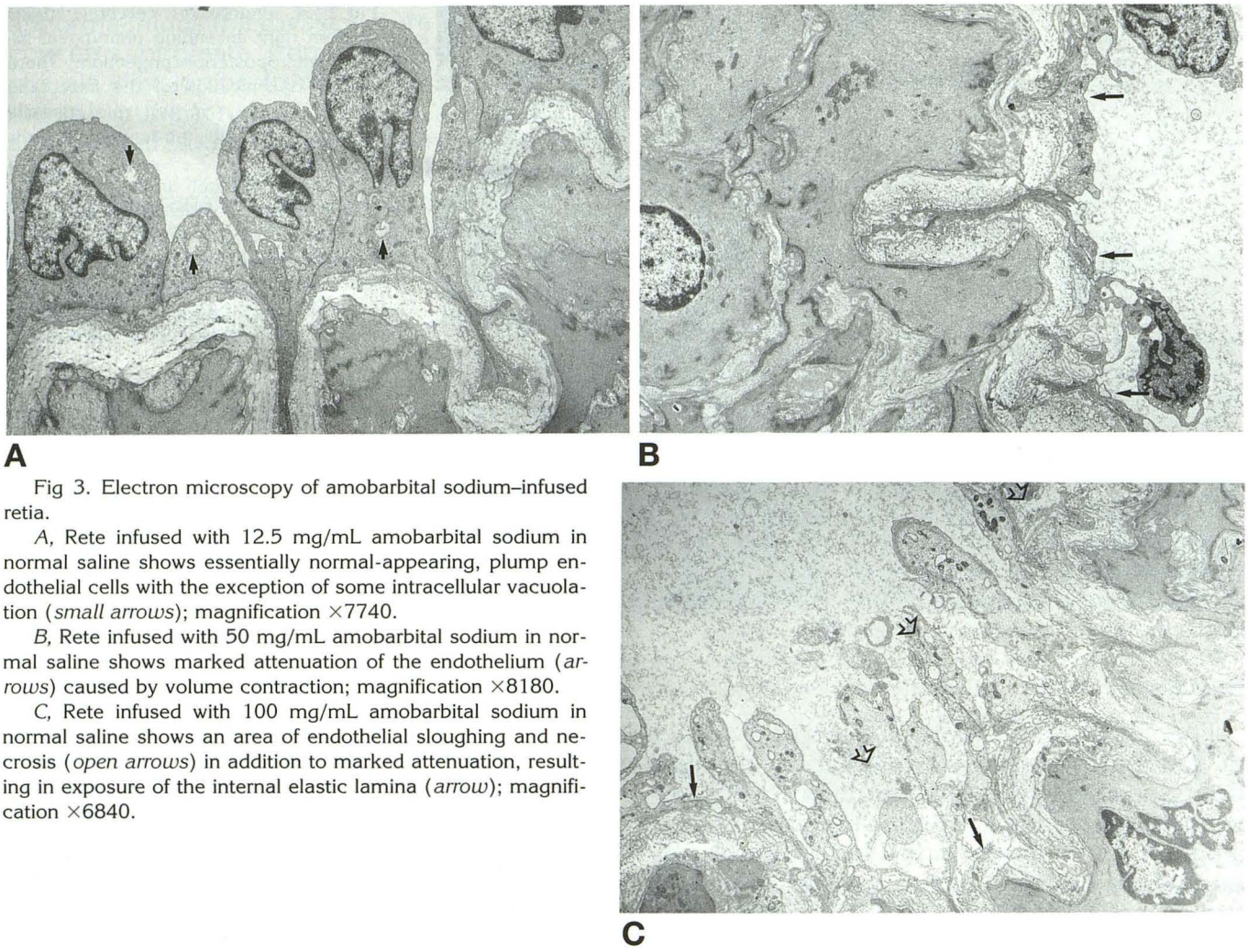

Fig 3. Electron microscopy of amobarbital sodium–infused retia.

A, Rete infused with 12.5 mg/mL amobarbital sodium in normal saline shows essentially normal-appearing, plump endothelial cells with the exception of some intracellular vacuolation (*small arrows*); magnification ×7740.

B, Rete infused with 50 mg/mL amobarbital sodium in normal saline shows marked attenuation of the endothelium (*arrows*) caused by volume contraction; magnification ×8180.

C, Rete infused with 100 mg/mL amobarbital sodium in normal saline shows an area of endothelial sloughing and necrosis (*open arrows*) in addition to marked attenuation, resulting in exposure of the internal elastic lamina (*arrow*); magnification ×6840.

Electron microscopy of both amobarbital sodium–infused and control retia showed varying degrees of cytoplasmic vacuolation within the endothelium. The extent of vacuolation did not appear to correlate with the type of infusion used. Vacuolation usually was seen in otherwise normal-appearing intima (Fig 3A).

Retia infused with 12.5 mg/mL amobarbital sodium in sterile water and saline and 50 mg/mL in sterile water showed normal endothelium with the exception of the above-described vacuolation. However, characteristic ultrastructural alterations of the retial intima were seen in seven specimens infused with higher tonicities of amobarbital sodium solution (50 mg/mL in normal saline [712 mOsm/L], 100 mg/mL in both sterile water and normal saline [808 and 1132 mOsm/L]). Milder alterations were seen in the retia infused with an amobarbital sodium solution tonicity of 712 mOsm/L. These changes consisted of areas of segmental thinning and attenuation of the endothelium (Fig 3B). At a tonicity of 808 mOsm/L the endothelium appeared more attenuated and had some areas of localized sloughing, although extensive denuding was not seen. The most severe changes were seen in the three specimens infused with an amobarbital sodium solution tonicity of 1132 mOsm/L, in which there was segmental endothelial necrosis and sloughing, as well as intraluminal necrotic cellular debris (Fig 3C). Despite the areas of severe endothelial damage seen in these retia, the underlying internal elastic lamina and superficial smooth muscle cells of the tunica media remained intact.

Discussion

Endovascular embolization of cerebral AVMs has become increasingly more effective and safe. This is in large part because advance-

ments in microcatheter technology permit superselective catheterization of cerebral arteries supplying an AVM. Pretherapeutic superselective angiography provides detailed anatomic and hemodynamic information about cerebral AVMs that is often unavailable from routine selective angiography. This information is valuable for therapeutic decision making when either endovascular embolization or surgical resection are being considered (3, 4). It is well known, however, that superselective angiography of AVMs frequently cannot detect small arterial branches, arising from a feeding pedicle, that are supplying normal adjacent brain. Embolization of these nutrient arteries can lead to untoward ischemic complications if this region of brain is functionally important. Conversely, superselective angiography will sometimes demonstrate small normal pial branches arising from a feeding pedicle, which may not supply eloquent cortex. Demonstration of these vessels may erroneously deter one from performing therapeutic embolization through such a feeding pedicle.

Thus, provocative testing with certain barbiturates of intermediate and short duration, such as amobarbital sodium (Amytal Sodium) and methohexital sodium (Brevital Sodium), have been increasingly used in conjunction with superselective angiography to improve the margin of safety for cerebral AVM embolization (1–7). Despite the increased use of superselective provocative testing, a detailed understanding of the pharmacology and physiology of cerebral intraarterial infusions of barbiturates is lacking. This incomplete understanding, combined with previous anecdotal reports of adverse reactions, has produced some concern related to potential damaging effects of superselective intraarterial infusions of amobarbital sodium on the cerebral microvasculature (3, 8).

Theoretically, such cerebral microvascular insults may have serious consequences, including interruption of the blood-brain barrier, acute thrombosis, vasospasm, perivascular inflammatory response, and diapedesis. These pathophysiologic processes can result in transient or permanent neurologic deficits caused by neurotoxicity, ischemia, and hemorrhage.

A swine endovascular embolization model was chosen to test possible microvascular toxicity of superselective infusions of amobarbital sodium because the rete mirabile is an excellent source of well-defined microvasculature. The rete mirabile is a plexiform network of interconnected microarteries in the size range of 50 to 250 μm that connects the external carotid circulation to the cerebral circulation. The retial system of swine is readily accessible by standard percutaneous coaxial catheterization techniques used in endovascular embolotherapy. This feature in combination with the unique anatomic arrangement and basic histologic construction of the rete (which resembles the nidus of an AVM) has made the swine an excellent in vivo AVM model for testing the efficacy and histotoxicity of new embolic agents (13–15). Consequently, this in vivo model appeared to be readily applicable to the study of potential microvascular histotoxicity of superselective infusions of amobarbital sodium.

In theory, there are four possible mechanisms of acute cerebral microvascular insult that may occur by a superselective infusion of a pharmacologic agent such as amobarbital sodium. First, it is possible that the injected amobarbital sodium solution can precipitate, resulting in thromboembolism within the infused microarterial bed. Second, it is possible that intraarterial infusions of barbiturates may exert a direct stimulatory effect on vascular smooth muscle. This vasomotor stimulation could produce vasospasm, leading to either temporary or permanent ischemic insult to the brain. Third, it is possible that superselective infusions of amobarbital sodium exert a widespread and severe toxicity to the tunica intima and tunica media of exposed microvasculature. This could produce angionecrosis with resultant thrombosis and/or rupture of affected vessels in a short-term setting and vasculitis in a long-term setting. Finally, it is possible that microvascular injury is initiated by a more limited degree of toxicity affecting only the endothelium. Endothelial cell damage could directly or indirectly initiate a variety of significant pathophysiologic events, including endothelial denuding, release of vasoactive substances (eg, endothelin and thromboxane), inhibition of prostacyclin, and release of mitogenic cytokines (eg, platelet-derived growth factor). These events in turn can either produce acute vasospasm and thromboembolism or intimal proliferation and encrustation in a long-term setting.

Previous studies have shown that concentrated solutions of amobarbital sodium (>100 mg/mL) mixed with saline may spontaneously precipitate and thus potentially cause thrombo-

embolism within an injected vascular bed (17). However, spontaneous precipitation at the concentrations currently in use clinically (10 to 15 mg/mL) has not been reported (3, 8). Monsein et al (8) have also shown that amobarbital sodium solutions should not be mixed with ionic contrast media, because doing so will produce an acid-base reaction with resultant precipitation. In the current study, we avoided exposing the amobarbital sodium solutions to any type of contrast medium by prior flushing of the microcatheters with normal saline. Visual inspections of the solutions before administration showed no spontaneous precipitation. No excessive thromboembolic phenomena were observed on histologic comparison of the amobarbital sodium–infused retia to controls, suggesting that precipitation of the amobarbital sodium solutions was not a problem in our study.

It has been shown previously that the occasional thrombi and foreign body emboli we observed in both amobarbital sodium–infused and saline/sterile water–infused retia are commonly seen after angiography and endovascular embolization. It is believed that these findings are caused by a combination of contaminants in the injected contrast media and microthrombotic phenomena developing around the tip of a catheter (18–20). Because there appeared to be no difference in the extent or frequency of these findings between experimental and control groups, we conclude that no significant thromboembolic histopathology occurred when various concentrations of amobarbital sodium were infused.

Although previous studies have shown that barbiturates can have both excitatory and inhibitory effects on vascular smooth muscle, it is uncertain what, if any, vasoactive effects amobarbital sodium has at the dosages and concentrations commonly used clinically and in this study for superselective intraarterial infusion. It is well known that acute intoxication with barbiturates used in anesthesia (eg, thiopental sodium) can lead to cardiovascular collapse, although this has been mostly attributed to a combination of peripheral vasodilation caused by decreased sympathetic tone and myocardial depression (21). Several in vitro studies have shown that various commonly used barbiturates (including amobarbital sodium) at relatively high concentrations (10^{-3} to 10^{-4} mol/L) exert a direct vasomotor inhibition of smooth muscle (22–26). A few in vitro studies have shown that certain types of barbiturates also can have direct contractile effects. Edney and Downes (26) showed that certain epileptogenic barbiturates (but not anesthetic barbiturates) can have a powerful vasoconstrictive effect. Another study by Moriyama et al (25) showed that thiamylal sodium and thiopental sodium paradoxically caused vasoconstriction at low concentrations (10^{-4} to 10^{-5} mol/L) and profound vasodilatation at higher concentrations (10^{-1} to 10^{-3} mol/L). However, no in vitro studies using amobarbital sodium have shown a direct vasomotor stimulatory effect. A clinical study by Zenteno et al (paper presented at the 29th Annual Meeting of the American Society of Neuroradiology, Washington, DC, June, 1991) showed that increases in intrapedicular pressure after superselective injection of amobarbital sodium may be caused by reactive vasoconstriction of normal cerebrovascular beds that are invisible by superselective angiography. They suggested that this reactive vasoconstriction may be the consequence of a direct excitatory effect on microvascular smooth muscle. Although far from conclusive, the results of our study do not support the idea of a direct vasomotor stimulatory effect of amobarbital sodium, because vasospasm induced by superselective amobarbital sodium infusions at the highest concentration used (100 mg/mL) only occurred when the carrier solution was normal saline (ie, no vasospasm occurred at the same concentration of amobarbital sodium dissolved in sterile water). This suggests that an alternate mechanism of vasospasm may be responsible. If superselective intraarterial infusions of amobarbital sodium (in the concentration range of 10 to 100 mg/mL) were to have any direct vasoactive effect, we suggest that based on the previously cited in vitro studies, this effect most likely would be inhibitory in nature, because relatively high local concentrations of the drug could be achieved.

The results of our study and those of others do not support the possibility of severe, generalized angiotoxicity of superselective injections of amobarbital sodium. We found that no "short-term" or "long-term" histologic specimen of retia infused with various concentrations of amobarbital sodium showed evidence of severe angiotoxicity. Even at a concentration of 100 mg/mL amobarbital sodium, which is eight times the usual clinical concentration, there was no histologic evidence of disruption

of internal elastic lamina, mural necrosis, or vasculitis, which are characteristics of severe angiotoxicity.

The most plausible explanation for any potential microvascular insult induced by superselective injection of amobarbital sodium would be on the basis of some type of endothelial injury. Theoretically, this can occur from either hyperalkalinity or hyperosmolality of these solutions.

Some previous reports of acute vasospasm occurring after intraarterial injection of various barbiturates have suggested that this problem may be caused by the hyperalkalinity of these solutions, although no substantial evidence has been provided (5, 6, 12, 20). However, the results of one recent study (7) and our findings do not support this contention. Peters et al (7) showed that despite the hyperalkalinity (pH 10.6 to 11.6) of dilute solutions of methohexital sodium (≤1%), no angiographic or clinical evidence of vasospasm occurred after superselective intracranial injection. These authors noted further that this pH range was similar to that of amobarbital sodium solutions used clinically. Specific measurements of the pH of amobarbital sodium solutions used for intracranial injection have been reported by Monsein et al (8) in which a concentration range of 27 to 83 mg/mL produced a corresponding pH range of 8.74 to 10.29.

Although we did not measure the pH of various amobarbital sodium solutions used in our study, it is likely that the range was similar to that described above. It may be further assumed that the alkalinity of these solutions mixed with normal saline would not substantially differ from those mixed with sterile water at a given concentration of amobarbital sodium. If this is true, the role of hyperalkalinity in producing endothelial injury cannot explain (*a*) the ultrastructural changes observed only in specimens infused with solutions mixed in normal saline at 50 mg/mL, (*b*) the most severe ultrastructural changes that occurred at concentrations of 100 mg/mL amobarbital sodium mixed in normal saline, and *(c)* angiographic evidence of vasospasm that only occurred at concentrations of 100 mg/mL amobarbital sodium in normal saline.

The current study showed a strong relationship between higher tonicity of amobarbital sodium solutions and both angiographic findings of vasospasm and ultrastructural changes in the endothelium. Such results are consistent with a hyperosmotic mechanism of endothelial toxicity, which produces so-called osmotic shock (3). A tonicity-dependent effect on the extent of ultrastructural alterations was seen after an apparent threshold of 50 mg/mL in normal saline (712 mOsm/L) was reached. At this tonicity milder ultrastructural alterations were seen, consisting of flattening and attenuation of the endothelium. This finding suggested that significant volume contraction of the cells occurred because of dehydration. At the other end of the spectrum, amobarbital sodium solutions of 100 mg/mL in normal saline (1138 mOsm/L), which is approximately four times that of normal serum, produced the most severe ultrastructural alterations of the endothelium. These changes mostly consisted of areas of endothelial necrosis and sloughing. It was also only at this highest tonicity that significant angiographic vasospasm occurred, which correlates well with the more severe ultrastructural alterations of the endothelium.

The finding of cytoplasmic vacuolation in both amobarbital sodium-infused and control retia was puzzling and cannot be readily explained. It is possible that this abnormality was caused by rapid fluctuations in intracellular water content that may have occurred when the endothelium was sequentially exposed to solutions of varying tonicity used during the angiographic (eg, heparinized saline flush, contrast agent) and infusion portions of the study.

We have previously used amobarbital sodium solutions mixed in normal saline at a concentration of 12.5 mg/mL for superselective provocative testing of more than 200 patients. This concentration of amobarbital sodium produces a tonicity of 409 mOsm/L, which is considerably less than the tonicity of a commonly used nonionic contrast agent for cerebral angiography (iopamidol [Isovue] 300; 616 mOsm/L). We have never encountered any adverse effects of superselective infusion with this concentration of amobarbital sodium solution, which probably can be attributed to its relatively low osmolality.

It is also likely that amobarbital sodium solutions used for provocative testing by intracarotid injection (ie, Wada test) are well within the range of safe tonicities suggested by this study. Typical dosages of 125 to 150 mg of amobarbital sodium are usually dissolved in a carrier solution of 8 to 10 mL of either sterile

water or normal saline, resulting in a tonicity range of approximately 101 to 460 mOsm/mL. We did not detect significant endothelial ultrastructural changes until a tonicity of 712 mOsm/L was reached. The potential risk of injection of these amobarbital sodium solution concentrations is further reduced by the likely rapid dilutional effect that occurs when injection is made into a large-caliber vessel with relatively large volumetric blood flow, such as the internal carotid artery.

In conclusion, this study suggests that the concerns for inducing significant damage to cerebral microvasculature by intraarterial injection of amobarbital sodium solution at the currently recommended concentrations and doses may be unjustified. Concentrated amobarbital sodium solutions (100 mg/mL) mixed in normal saline produce an extremely hypertonic solution, which when infused by superselective injection into microvasculature can cause significant endothelial damage with resultant acute vasospasm.

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