Pathology of arteriovenous malformations embolized with isobutyl-2-cyanoacrylate (bucrylate)

Report of two cases

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There is controversy as to the possible toxic effects of isobutyl-2-cyanoacrylate (bucrylate) when this substance is used for purposes of therapeutic embolization. Two cases are presented in which cerebral arteriovenous malformations were resected, one 42 days and the other a year after bucrylate embolization. In both, pathological examination revealed a brisk intimal foreign-body giant-cell reaction wherever bucrylate was present in a vessel, along with chronic inflammation in the vessel walls and adjacent brain parenchyma. The findings are discussed in the light of other observations on the histotoxicity of bucrylate.

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INTERVENTIONAL radiology as one therapeutic tool in the treatment of several types of lesion, including those in the brain and spinal cord, is now well established. Both non-neoplastic and neoplastic structures in the central neuraxis and elsewhere may be approached by skillful catheter control, and they or their feeding vessels embolized with any one of a variety of synthetic or natural agents. These include Gelfoam, Silastic, wool coil, silicone and low-viscosity silicone rubber, autogenous clot, muscle or dura, Ivalon (polyvinyl alcohol), and Oxycel (oxidized cellulose). The indications and contraindications for use of these techniques, as well as resultant beneficial effects and complications, have been discussed. Embolotherapy with detachable and calibrated-leak balloons has been used to treat both encephalic and visceral lesions. Refinement of the relevant methods is evolving at a fast pace. Review of an extensive experience with cerebral arteriovenous malformation (AVM) embolization, using the transfemoral flow-directed technique or direct selective feeder embolization at craniotomy, has recently been provided by Drake.

One of the newest materials to be used for purposes of therapeutic embolization is isobutyl-2-cyanoacrylate (bucrylate). This is a liquid adhesive material of low viscosity that polymerizes rapidly upon contact with blood. Its rate of polymerization can be titrated by the addition of varying amounts of iophendylate (Pantopaque). This substance has obvious possible uses in obliterating the blood supply to tumors, vascular malformations, and large bleeding vessels. It has been used in the central nervous system as the primary treatment modality for a large spinal AVM, and as an adjunct to neurosurgery during the excision of cerebral AVM's. Its function in the latter cases was to reduce blood flow to the AVM's, and thereby to decrease the total blood loss during surgery. Treatment of an aneurysm of the vein of Galen in a 6-year-old child using only this means was reported by Debrun, et al. Three patients have had successful occlusion of carotid-cavernous fistulas with preservation of carotid artery blood flow. It has also been used in the treatment of visceral lesions. Investigators who have used bucrylate point out its several advantages over other embolic substances, although it must be used with caution.

Visceral transcatheter occlusive therapy with bucrylate for the treatment of uncontrolled hemorrhage has been described. Pathological examination of the
embolized and adjacent tissues has been carried out in patients who underwent autopsy following the procedure.

This report documents two patients in whom cerebral AVMs were resected following therapeutic embolization with bucrylate. The rather unique pathological findings are described and compared with those found after visceral embolization and in the experimental setting.

Case Reports

Case 1

At the age of 33 years, this woman had been investigated for headache and found to have a deep left occipital AVM, which was partially removed. Nineteen years later, in November, 1976, she suffered a subarachnoid hemorrhage (SAH). Approximately 2 1/2 years later, she was referred to the University Hospital for investigation. Cerebral angiograms performed in June, 1979, revealed a recurrent large left occipital AVM, supplied by the left posterior cerebral, superior cerebellar, and middle cerebral arteries, and the left superficial occipital, superficial temporal, and middle meningeal arteries. There was also a vascular contribution from branches of the right external carotid artery. On June 20, 1979, the left occipital and middle meningeal arteries were embolized with Ivalon and bucrylate through the external carotid artery. Five days later, embolization of the right posterior and middle meningeal arteries was carried out using bucrylate, and the right occipital artery was embolized with Ivalon. Angiograms after embolization revealed that the right occipital artery was only partly occluded and a branch feeder from the right middle meningeal artery was still patent. Bucrylate embolization of the AVM was attempted via the left posterior cerebral artery on June 29 and July 3. During the latter attempt, a Kerber balloon-catheter being used for the procedure burst in this artery, with rapid embolization of the AVM, but probably some passage of bucrylate into the venous system and return to the lungs. On July 9, 19 days after the initial embolization, a left external carotid angiogram showed that all branches from this vessel to the AVM were occluded. A left vertebral angiogram at the same time revealed that the main trunk of the left posterior cerebral artery was occluded, but there were still two or three patent branches feeding the malformation. A right internal carotid angiogram revealed that both pericallosal arteries supplied the AVM. Finally, the right external carotid artery was catheterized, and feeders from the right middle meningeal and occipital arteries were occluded with Ivalon. The AVM was excised at craniotomy on August 1, 41 days after the initial embolization, and the patient has remained well, with only a persistent right homonymous hemianopsia.

Case 2

This 34-year-old airline pilot was admitted to University Hospital in July, 1976, with a 1-year history of difficulty in judging distances when landing airplanes. He had also noted flashing lights in both eyes and for 2 to 3 months had experienced worsening incoordination and weakness of his left hand. Examination of the patient revealed only mild dysarthria, a mild left hemiparesis (greater in the face than the arm or leg), and hyperreflexia on the left side. Cerebral angiograms showed a giant aneurysm at the junction of the basilar artery and P1 segment of the right posterior cerebral artery, a large right parieto-occipital AVM supplied by the middle and posterior cerebral arteries and the pericallosal artery, and two small right carotid artery aneurysms.

At frontotemporal craniotomy on July 19, 1976, the large basilar tip aneurysm was successfully clipped. Postoperative angiograms confirmed obliteration of the aneurysm, and there was decreased blood flow through the AVM. On August 20, a right parieto-occipital craniotomy was carried out, and the AVM directly embolized with Gelfoam stained with Ethiodan, through one of the right middle cerebral feeding vessels. In January, 1977, the patient was neurologically intact apart from a small inferior quadratic sector defect in the left visual field, and there was a partial right oculomotor palsy. Angiograms confirmed that the AVM was in large part thrombosed.

In August, 1978, the patient again experienced flashing lights in his visual fields, and blurred vision, as well as transient clumsiness of the left hand. Angiograms in January, 1979, showed the right occipital artery to be enormously enlarged and filling part of the AVM through the skull above the inion. The AVM was also filling from a recanalized right posterior cerebral artery. Successful embolization of the right occipital artery was carried out with 0.5 ml of bucrylate. The patient was readmitted in January, 1980, with complaints of persistent diplopia and flashing lights in the left visual field. The parieto-occipital AVM was patent and still fed by middle cerebral branches, with retrograde recanalization of the right posterior cerebral artery. The right occipital artery remained occluded. A large left occipital artery feeder to the AVM was catheterized and 0.5 ml bucrylate injected, with thrombosis of the artery. The AVM was ultimately excised on February 8, 1980, through a right posterior bone flap, and the patient has remained well. In this case, as in the previous one, tantalum was injected together with bucrylate, as a radiopaque marker.

Pathologic Findings

Microscopic examination of the AVM in each case revealed that many, although not all, vascular channels were thrombosed and contained a particulate black substance, representing the bucrylate-tantalum mixture (Fig. 1). No particular size of vascular channel seemed especially prone to undergo thrombosis, and
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widely patent vessels could easily be identified in both pathological specimens. Within the lumina of the vessels, there was a marked intimal histiocytic and foreign-body giant-cell reaction adjacent to the bucrylate-tantalum mixture (Figs. 2 and 4). Also, within the walls of the embolized AVM channels, and extending into the surrounding gliotic brain parenchyma, a variable but focally marked chronic inflammatory reaction was present (Fig. 3), with abundant mononuclear inflammatory cells including lymphocytes, plasma cells, and histiocytes (Fig. 4). In the parenchyma, no foreign-body giant cells or particulate material were observed. The histological changes within the AVM's were otherwise as expected for malformations of long standing, with marked astrocytosis in the parenchyma, variable thickening of vessel walls, and focal mural calcification (Fig. 1). Because the AVM is, by definition, a lesion in which there is a variable presence of elastica from vessel to vessel, destruction of this imperfect elastica by the inflammatory reaction could not be accurately assessed.

Despite the fact that in both patients, embolization with other synthetic materials had been undertaken (Ivalon in the first case, Gelfoam in the second), no trace of either substance was encountered in the histological preparations. In the first patient, since Ivalon embolization was primarily into the feeding vessels rather than the AVM, the material may have lodged within these and failed to reach the AVM itself. It is not surprising, in view of the multiple feeders to each AVM (only a few of which were embolized), that many vascular channels showed no trace of the bucrylate-tantalum mixture.

Discussion

The lively debate that has arisen around the potential histotoxic effects of bucrylate is a critical one in view of the possible therapeutic uses for this substance. The two most recent studies to focus on this matter have been those by Freeny, et al., and White, et al. The former group undertook detailed radiographic and pathological follow-up review in 14 pa-

![Fig. 1. Case 1. Photomicrograph showing a portion of the embolized arteriovenous malformation. Three vascular channels contain the bucrylate-tantalum mixture and have undergone thrombosis. In and around the vessels, there is a mononuclear inflammatory cell infiltrate as in the neuroglial parenchyma (arrows). Some vessels have heavily calcified walls. H & E, × 49.](image-url)
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Fig. 2. Case 1. Photomicrograph of vascular channels of varying diameter containing the bucrylate-tantalum mixture. There is a pronounced intimal foreign-body giant-cell reaction around the embolic material (arrow) and scattered lymphocytes in the vessel walls and adjacent parenchyma. Some vessels (such as seen at upper right) contain no trace of foreign material. H & E, × 126.

Patients treated by visceral transcatheter occlusive therapy with bucrylate for a variety of abdominal lesions, including hepatocellular carcinoma with a bleeding duodenal ulcer, hepatic cavernous hemangioma, Mallory-Weiss tear, and five cases of gastroesophageal varices. In six patients, who subsequently died and came to necropsy, the embolization had been carried out from 2 to 196 days before death. Yet the pathological findings were quite uniform, consisting of a mild histiocytic foreign-body giant-cell reaction to bucrylate. This reaction was confined to the vessel lumina in all cases, without extension into the surrounding parenchyma. There were no ischemic or inflammatory reactions in the peripheral organs, and apparently insignificant mural damage to the blood vessels was involved. In three patients (with histological examination 7, 18, and 196 days after embolization), there was no intimal reaction at all.

By contrast, White, et al.,27 embolized the gastro-splenic and hepatic arteries of pigs, and performed histopathological studies 3 to 5 months later. Bucrylate was surrounded by giant cells and organized thrombus, but there was also variable chronic inflammation in the thrombus and surrounding tissues, with focal disruption of the internal elastic lamina. They also found healed gastric ulcers beneath the area of occlusion, splenic and duodenal infarcts, hepatic abscesses, and biliary cysts surrounded by scars from hepatic infarction. Within these secondary lesions, there were often small blood vessels containing bucrylate with giant cells, and chronic inflammation in nearby tissues. Freeny, et al.,29 have suggested that the experimental data do not relate directly to the human situation, because of unique anatomical features in the porcine vascular tree, and a possible species variation in reaction to bucrylate.

Zanetti and Sherman28 utilized bucrylate to occlude surgically constructed vein pouch aneurysms in dogs. Successful thrombosis of aneurysms was achieved; at 1, 2, and 3 months after embolization, the mouths of
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Fig. 3. Case 2. Photomicrograph of two occluded vessels (arrows) containing bucrylate-tantalum, surrounded by foreign-body giant cells. Chronic inflammation is noted in and around the vessel walls. Some vessels have thickened walls, and there is reactive gliosis in the surrounding parenchyma. H & E, × 126.

The aneurysms had endothelial-lined fibrous walls. The interstices of the bucrylate material contained fibrous tissue and scattered foreign-body giant cells. The aneurysm walls consisted of fibrous scars. The effects of the material did not extend beyond the original venous graft. In a related experiment, injection of normal renal arteries with bucrylate caused initial endothelial damage, but left the media and adventitia unaffected for as long as 2 to 3 months after injection.

A recent note has referred to the finding that intravascular bucrylate in primates causes a "vigorous inflammatory reaction dominated by foreign-body giant cells," without further details of pathological observations. Experimental injection of bucrylate into renal arteries of dogs has produced, in addition to occlusion and infarction, a variable inflammatory reaction, ranging from minimal to severe, with necrosis of vessel walls, acute inflammation, and a foreign-body reaction that extended into adjacent tissues.

The time interval between initial bucrylate embolization and removal of the AVM in our study was 42 days in the first patient, and over 1 year in the second. Curiously, neither AVM showed evidence of the presence of either Ivalon or Gelfoam, the other materials that had been used for therapeutic embolization. Barth, et al., have found that 4 months after visceral embolization with Gelfoam, no trace of the material or an inflammatory vascular reaction to it was present. They have cited a previous study in primates which demonstrated the peak foreign-body reaction to Gelfoam at 20 days after application, with disappearance of the substance by 45 days. We, therefore, attribute the inflammatory response as noted to the bucrylate, since tantalum is an inert radiopaque tracer metal.

One must, therefore, conclude that bucrylate in this situation is capable of producing a mild chronic parenchymal inflammatory response in tissues adjacent to the vessels that it has occluded. From the surgical specimens examined, the reaction does not appear to be as profound as that described by others. Clinically, the patients have done well and, on these
grounds, there is no reason to believe that the embolic material has lodged in vessels outside the AVM to cause significant cerebral infarcts. However, "silent" small cerebral infarcts may have occurred without clinical sequelae. It is also impossible to rule out the passage of microscopic amounts of material into the systemic venous circulation with deposition in the lungs, a known risk with other substances.

An AVM, although it contains neuroglial elements, is a pathological entity, and our results cannot be taken to infer a specific effect of bucrylate on normal brain tissue, any more than the conclusions of others should be extrapolated to normal viscera. In fact, there may be abnormal permeability properties of the vascular channels within the malformation that facilitate an inflammatory reaction to bucrylate. Debrun has stressed that a brisk inflammatory reaction may indeed expedite thrombosis of pathological blood vessels within an AVM. Nevertheless, we feel it important to report the findings, which we believe to be the first made in relatively long-term pathological follow-up review after bucrylate embolization of encephalic vascular malformations.

It is also of interest to contrast the histological effects of bucrylate with those of other embolic substances, such as Gelfoam and Ivalon. The latter has been shown to induce the formation of dense fibrous connective tissue, as well as rare giant cells, in and around the sponge spicules, but relatively mild inflammation in or around regions of thrombosis. Undoubtedly, as embolization procedures become more commonplace, and embolized organs become available for histological analysis, our understanding of the interesting effects of these materials on tissue will expand. Careful histopathological studies are of the greatest importance, as the pathological changes may be qualitatively and quantitatively different from those seen in experimental situations.

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References


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