Infusing Doubt into the Efficacy of Papaverine

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Since the first report, in 1984 by Zubkov (1), of the use of intracranial balloon angioplasty for subarachnoid hemorrhage–induced cerebral vasospasm, endovascular techniques have gained acceptance as valuable therapies in the treatment of vasospasm resistant to conventional therapies (2–6). Although angioplasty and intraarterial papaverine infusion are both used by many practitioners, the role of angioplasty seems better defined than that of papaverine. This likely relates to a perception that the risk:benefit ratio of angioplasty is more favorable than that of papaverine. Granted, the risks of angioplasty, which include vessel perforation, can be serious. However, the benefit of angioplasty has been documented through clinical and angiographic response as well as by single-photon emission computed tomography and quantitative cerebral blood flow measurement (2, 6, 7). Furthermore, the effect of angioplasty on vessel diameter is usually permanent (2).

The risk:benefit ratio of papaverine therapy has been difficult to establish; both the reliability and the durability of papaverine-induced vessel dilation appears less certain than that typically achieved with angioplasty. Indeed, the reported frequency of clinical response to papaverine has been as low as 25% (4). Improved understanding of the factors that govern a vessel’s response to papaverine infusion would allow better stratification of the expected utility of the treatment, which in turn would allow better definition of the drug’s risk:benefit ratio.

Studies in multiple animal models have suggested that the response of a spastic vessel to the vasodilatory effects of papaverine depends on the duration of the spasm (8–10). Using a rabbit model of cerebral vasospasm, Vorkapic et al (10) showed that the response to papaverine was excellent over the first 3 days after induction of vasospasm, but that a progressive decline in responsiveness to papaverine was noted from day 3 until day 9 after spasm induction. Macdonald et al (8), using a canine model, showed diminished response to papaverine 10 to 14 days after induction of vasospasm, compared to 4 to 7 days after induction. These data suggest that the pathophysiology of arterial narrowing early in vasospasm consists of smooth muscle contraction; later, the vessel narrowing probably results from arterial wall fibrosis, edema, inflammation, or intimal proliferation (8).

The study by Fujiwara et al (11) in this issue of AJNR adds further experimental evidence not only that the response of vasospasm to papaverine is transient but also that it declines with increasing duration of vasospasm. These authors present a well-conceived experiment to address both issues. Although the number of animals is small, there is little variation in results among the subjects. Furthermore, the histologic sections add further evidence that morphologic changes within the vessel wall increase with increasing duration of vasospasm. It is unfortunate, however, that repeat lumen measurements could not be carried out 24 hours after papaverine infusion, and that the transient effect of papaverine was shown only by transcranial Doppler.

The major drawback of the study under consideration is that, like most previous animal studies, attention was focused on large, proximal arteries rather than smaller, distal arteries (11). In clinical practice proximal vasospasm is treated by balloon angioplasty. Papaverine therapy for proximal spasm is instituted only when angioplasty is not technically feasible. The primary role for papaverine is in treating distal vessels beyond the reach of angioplasty. These distal vessels were not evaluated with either angiography or histologic analysis in the study by Fujiwara et al (11). Morphologic changes noted...
in large, proximal vessels do not necessarily reflect what is occurring in smaller, distal vessels. Indeed, Bevan et al (9) showed in monkeys that 6 days after spasm induction, proximal vessels were narrowed by an inflammatory response while distal vessels were narrowed by increased vascular tone, which may respond favorably to papaverine.

Should one conclude, based on the animal data, that the benefits of papaverine therapy will be transient and limited only to spasm occurring early after subarachnoid hemorrhage? Probably not, because clinical data do not necessarily corroborate the experimental data. Granted, an early clinical report suggested that early vasospasm might be more responsive than late spasm to the effects of papaverine (5). However, that report was based on only two patients. Multiple subsequent series have shown no difference in the time after subarachnoid hemorrhage between groups of patients who did and did not respond to papaverine (3, 4, 7, 12). Also, Kassell et al (4) noted excellent responses to papaverine in two patients treated again 5 days after initial papaverine therapy. Furthermore, a recent series noted no evidence for recurrent spasm among early responders, suggesting that even though the pharmacologic duration of action of papaverine is relatively short, prolonged clinical response is achievable (12). Therefore, even though mounting experimental evidence suggests that changes occur within the spastic vessel walls that should be unresponsive to pharmacologic therapy, papaverine remains an acceptable therapy in selected patients.

There is much yet to be understood about the mechanism of action of papaverine. For instance, it is not clear why the rate of clinical response to papaverine is only one half that of the angiographic response in most series (4, 12, 13). Also, the spectrum of potential adverse reaction is broad, including transient neurologic dysfunction, increased intracranial pressure, mydriasis, precipitation of the drug from solution, and, according to a recent report, paradoxical aggravation of vasospasm in response to papaverine (13–17). Even so, in our practice the routine use of papaverine remains an adjunct to balloon angioplasty in the treatment of refractory vasospasm.

References