Efficacy of Isradipine in Middle Cerebral Artery-Occluded Rats

To the Editor:

We would like to comment on the Short Communication by Marinov and Wassmann concerning effects of Isradipine (PN 200-110) in middle cerebral artery-occluded rats. First, the authors’ conclusion that PN 200-110 is ineffective in their model is based entirely on experiments made with a single dose of the drug. Although efficacy of a drug may be claimed with some confidence based on a single dose or regimen of application, this certainly is not the case for proving a drug’s ineffectiveness! In fact, we found it difficult to elucidate the exact dose regimen administered to the three different groups of rats. We assert that the rats were infused intravenously for 2 hours with PN 200-110 at a rate of 1 mg/ml/min, yielding a total dose of 0.24 mg/kg. The volume of solvent (saline, glucose, ethanol, polyethylene glycol 400) administered to the rats over the 2-hour period of infusion was unclear; was it 0.4 ml/hr to all rats, irrespective of weight (250–300 g), or was it 0.4 ml/hr/kg? Furthermore, we assume that 1 mg PN 200-110 was dissolved in 1 ml rather than 1 mg of 96% ethanol, which makes quite a difference concerning the total amount of ethanol infused.

Our second concern points the way in which the “relative infarct size” has been determined. Infarct size in control and PN 200-110–treated rats has been deduced in this study from the cross-sectional areas of only two coronal sections, which are only two mm apart, covering in fact only the middle part of the total infarct volume. Yet it is well known that in the rat strain used (Fisher 344), the infarct actually extends in the caudorostral direction over a distance of at least 8 mm (from 2.2 to 10.5 mm anterior to the intra-aural line). Therefore, the infarct size as determined in this article represents at best a very rough estimate of the total infarct volume, overlooking in particular the anterior and posterior border zones of infarction. Yet, it is exactly there, in the so-called penumbra, that the protective effects of drugs, be they calcium or NMDA antagonists, are most prominent. The final sentence of the discussion, in which it is stated that the drug (Isradipine, PN 200-110) had no protective action on the penumbra of the lesion, is inappropriate because this border region of the infarct was not adequately evaluated in the present study.

Another concern is the use of ketamine as anesthetic. Ketamine is a selective, noncompetitive NMDA antagonist which, like MK-801, might by itself substantially reduce the size of infarction already in the “control” and “placebo” groups.

We are in fact surprised that, despite our concerns, the authors find a 15% reduction (placebo, 9.49; PN 200-110, 8.08) in cortical infarct size with a dose of PN 200-110 of 0.24 mg/kg infused over 2 hours, since approximately this effect would have been predicted based on the dose–response curve we obtained in the same rat model.7 At a 10 times higher intravenous dose, a reduction in infarct size of approximately 60% would be expected, based on the previous studies, and, with the same variability (±10–20% SEM) and number of animals (n=7–8), even statistical significance should then be reached, necessitating a major revision of the conclusions drawn in this article!

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References


Cerebral Infarction, Livedo Reticularis, and Familial Deficiency in Antithrombin-III

To the Editor: A right-handed 34-year-old woman from the Marquesas Islands was hospitalized on April 14, 1990, for mixed aphasia and right palsy predominating on the face and upper limb. At the time of admission, she had two children and was 3 months pregnant. In the previous 6 months, she had suffered similar episodes transiently but had not sought medical attention.

Clinical examination showed a palmar erythema, a livid coloration of both inferior limbs, and cyanosis of the extremities. She had mild hypertension. Brain computed tomography was significant for recent superficial temporal ischemia and showed sequelae of ischemia in the territories supplied by the middle and posterior cerebral arteries. Ultrasound examination of the large neck vessels was normal; cerebral angiography was not performed because of the pregnancy. Echocardiographic examination revealed mitral valve prolapse. No thrombus was found in the cardiac cavities, and Holter monitoring was normal. The only sign of inflammation was the presence of circulating immune complexes.

Phospholipid antibodies were absent. Skin biopsy showed fibrosis of the chorion layer with thickening of some vessel walls but no inflammatory exudate. Coagulation tests revealed a type I quantitative deficit of antithrombin-III (AT-III) as follows: activity 0.44 IU/ml (normal, 1±0.2 IU/ml) and antigen 10 mg/dl (normal, 30±6 mg/dl). The dosages were carried out on three different specimens to confirm the diagnosis and to avoid a temporary deficit by consumption due to heparin treatment. Plasma AT-III assays were performed by chromogenic assay for AT-III activity (Stackrom AT III, Diagnostica Stago) and by radial immunodiffusion for AT-III antigen (Nor Partigen Antithrombin III, Behring) to allow for typing of the deficit.

The patient’s sister had had phlebitis twice during pregnancy with similar findings of AT-III activity (0.36 IU/ml) and AT-III antigen (15.6 mg/dl). Her younger brother also had a history of repeated thromboembolic disease of the lower limb. However, he
and the rest of the family were still in the Marquesas Islands and could not be examined. Heparin treatment (Calciparine, Du Pont) associated with AT-III was administered on April 27. Despite anticoagulant therapy, pulmonary embolism occurred, resulting in an abortion and inferior vena cava occlusion. Currently, the patient is taking oral anticoagulants and has speech and gait defects.

One of two etiologies may account for our patient’s manifestations. Sneddon’s syndrome is a rare clinical entity prevalent in younger women. Approximately 60 cases have been reported to date. The neurological clinical picture includes recurrent transient or permanent ischemic cerebrovascular attacks, fits, and deterioration of intellect. Livedo reticularis may precede neurological manifestations for many years.1 Many cases have included the presence of phospholipid antibodies,2 leading to the hypothesis of Sneddon’s syndrome as a phospholipid antibody disease.3 The association of Sneddon’s syndrome and mitral heart disease, as observed in our case, was also recently reported,2 but because the pathophysiology of this entity remains unclear, no specific treatment strategy has been developed.

A second possible etiology is familial AT-III deficiency, an autosomal dominant disorder that causes a predisposition to recurrent venous thromboembolic disease and arterial occlusion.4 Thromboembolic disease is frequently encountered during pregnancy in association with Sneddon’s syndrome or AT-III deficiency.5 To our knowledge, the association of Sneddon’s syndrome and a familial deficiency of AT-III has never been reported. The combination of livedo reticularis, mitral valve prolapse, and AT-III deficiency observed in our patient probably accounts for the multiple arterial and venous thrombi and the failure of anticoagulant therapy.

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Risk of Stroke in Idiopathic Hypertrophic Subaortic Stenosis

To the Editor:
The association between idiopathic hypertrophic subaortic ste-nosis (IHSS), more recently defined as hypertrophic cardiomyopathy, and cerebral ischemia has only rarely been appreciated,1,2 and IHSS has never been considered a high-risk disease for stroke. Russell et al3 have recently reported in Stroke an extremely high incidence of cerebral ischemic events (22%) in a large series of patients with IHSS followed for 6.5 years. In five patients, stroke was the presenting manifestation of IHSS. The authors conclude that patients with IHSS are at high risk for ischemic cerebrovascular complications. These new, interesting data are apparently in contrast with current cardiological opinion. Who is right?

In dealing with patients with cardiac disease and stroke, it is crucial to establish a cause-and-effect relationship between cardiac disease and cerebral ischemia. Besides presumptive clinical neurological criteria, the absence of atherosclerotic vascular disease based on cerebral angiography or carotid echotomography is an essential requisite for the diagnosis of cardiogenic cerebral embolism.4 It is likely that, following these criteria, a presumably cardioemboolic etiology of cerebral ischemia was consequently established in only nine patients in the series of Russell et al.3 Considering only these cases, the incidence of cerebral ischemic events approximates the figures reported in the literature.1-5-11 (Table 1). In the remaining patients with atheroembolic, atherothrombotic, or lacunar stroke, IHSS can represent only a coincidental finding. An advanced age at stroke and an extremely high prevalence of hypertension may represent the major risk factors for cerebral ischemia rather than IHSS itself. Moreover, in the presence of long-standing hypertension, whose prevalence in the series of Russell et al was as high as 69%, the diagnosis of IHSS may be complicated by a differential diagnosis of hypertensive heart disease.

But even considering only those nine patients with cardioembolic stroke or transient ischemic attack, the data reported by Russell et al3 are noteworthy, confirming our previous observations derived by a different approach to the problem. In a series of 380 consecutive patients (mean age 53.6 years) with cerebral ischemia who were referred to the Neurosurgical Department, embolic cardiac lesions were documented by two-dimensional echocardiography in 27 patients (7%); among these cases, six patients with IHSS were identified. In five cases, associated factors responsible for embolism were identified: paroxysmal atrial fibrillation in three patients, infective endocarditis with mitral valve vegetations in one, and evolution of IHSS into a dilatative form with intraventricular thrombus in one. In all cases, cerebral angiography or carotid echotomography excluded the presence of atherosclerotic vascular lesions.12

A careful analysis of larger series of IHSS reported in the literature demonstrates that the risk of cerebral embolism in IHSS is not negligible, occurring in 2–15% of patients, with an estimated incidence of embolism of 0.4–2.4% yearly. Nevertheless, the stratification of the embolic risk has not received much attention up to the present time. Russell et al3 deserve credit for stressing this aspect.

Idiopathic hypertrophic subaortic stenosis per se is not an embolic cardiac condition; the rapid flow and lack of opportunity for stasis do not predispose the patient to the formation of left ventricular thrombi. The risk of embolism is almost always related to the occurrence of atrial fibrillation, which occurs in 5–10% of patients with IHSS, usually late in the course of the disease.7,9,13 Similar findings resulted from the series of Russell et al (seven of nine patients). Infective endocarditis or evolution toward dilation with systolic dysfunction and congestive heart failure, which develops in about 10% of patients with IHSS, represent other major events predisposing patients to embolism. Left atrial enlargement, mitral annulus calcification, and low cardiac output can be invoked as contributing mechanisms. In Table 1 the incidence of atrial fibrillation, infective endocarditis, and embolism in larger series of IHSS is reported. The risk factors for embolism are specified in the last column.
Cerebral infarction, livedo reticularis, and familial deficiency in antithrombin-III.
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