Letters to the Editor

Efficacy of Isradipine in Middle Cerebral Artery-Occluded Rats

To the Editor:

We would like to comment on the Short Communication by Marinov and Wassmann1 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 assume that the rats were infused intravenously for 2 hours with PN 200-110 at a rate of 0.002 mg/kg/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 is 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 point concerns 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 known2 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. 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.34 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 antagonist5 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.67 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 aphasis 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, 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...
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