Application of a Rat Stroke Model for Preclinical Evaluation of Anti-Stroke Drugs: Noninvasive Monitoring with Comprehensive Magnetic Resonance Imaging

F. Chen[1], Y. Ni[1], N. Nagai[2], Y. Suzuki[2], D. Collen[2], G. Marchal[3]

[1]Radiology, Catholic University of Leuven, Leuven, Flamms Brabant, Belgium, [2]Center of Molecular and Vascular Biology, Catholic University of Leuven, Leuven, Flaams Brabant, Belgium, [3]Radiology, Catholic University of Leuven, Leuven, Flaams Brabant, Belgium

Background and Purpose

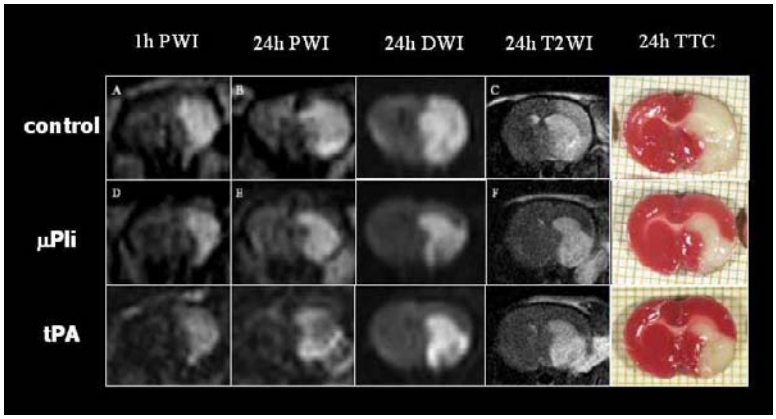
Clinically relevant animal models and noninvasive testing methods are essential for advanced drug development. This study was aimed at longitudinal evaluation of anti-stroke efficacy of a few thrombolytic agents including tissue plasminogen activator (tPA) and Microplasmin (μPli) in a novel rodent stroke model using comprehensive magnetic resonance imaging (MRI).

Materials and Methods

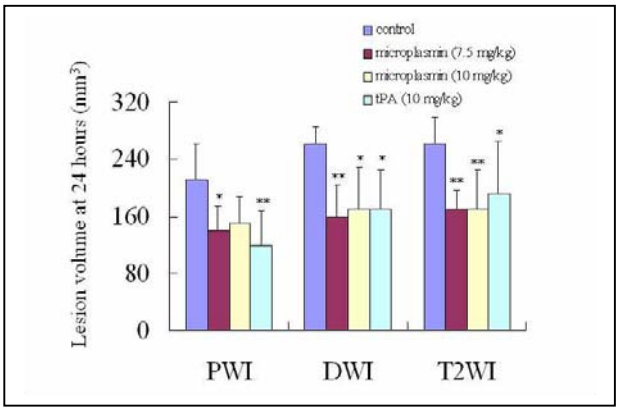
Photochemical thrombosis of proximal middle cerebral artery (MCA) was induced in 60 rats to simulate the most common stroke type in patients. Using a clinical 1.5 Tesla scanner, MRI of T2 weighted imaging (T2WI), diffusion weighted imaging (DWI), and particularly contrast enhanced perfusion weighted imaging (PWI) was performed to 1) determine adequate initial stroke size involving both cortex and striatum as criteria for eligible inclusion and 2) monitor infarct evolution in rats with and without anti-stroke treatment. The qualified animals were randomly divided into groups and double-blindly treated with intravenous injection of μPli at low dose of 7.5 mg/kg (group A, n=13) or at high dose of 10 mg/kg (group B, n=9), or tPA at 10mg/kg (group C, n=14), or equal volume of solvent (group D, n=13) 90 minutes after MCA occlusion. Brain tissue damage was compared among different groups at 1 hour (h) and 24 hours after MCA occlusion with in vivo MRI and postmortem 2,3,5-triphenyl tetrazolium chloride (TTC) staining, and further correlated with the neurological symptoms scored before sacrifice.

Results

Focal cerebral ischemic lesions at the MCA territory were detected with MRI in 100% of rats (60/60), among which about 812% (49/60) were included for the study. Compared to the control, the ischemic lesion volume was significantly reduced on PWI, DWI and T2WI after treatment of uPli or tPA at 24 h (Fig. 1); the relative cerebral blood volume and flow, PWI-DWI mismatch area in the ischemic region were decreased over the first 24h. The infarct volumes in μPli or tPA treated group A (180±30 mm3), B (160±62 mm3) and C (160±73 mm3) were significantly reduced in comparison with that in group D of controls (240±74 mm3), as proven by TTC staining at 24 h (Fig.1). The neurological deficits of Bederson score were also reduced from 6-9 in the control group to 3-8 in the treated groups. The intracerebral hemorrhage was more evident in group C than that in group A and B.



A



B

Fig.1 Effect in rats treated with mPli or tPA.
A: Compared to the control, the ischemic cortex was rescued as proven on MRI and TTC staining at 24 h.
B: Quantitative analysis, *p< 0.05, **p<0.01 vs control group.

Conclusions

Utilizing the rodent stroke model and available MRI facilities, the present experimental system proved to be beneficial for anti-stroke drug evaluation. Both thrombolytic drugs reduced cerebral ischemic damage and improved neurological dysfunction, but μPli appeared with less hemorrhagic risk than tPA.