**SB 234551 improves cortical collateral perfusion following permanent MCAO in the rat**

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**Introduction**

Endothelin-1, a key component of microcirculatory failure (1), has been reported to increase following ischemic or hemorrhagic stroke (2,3). The aim of the present study was to investigate region specific differences in cerebral blood flow following permanent middle cerebral artery occlusion (MCAO) in animals treated with placebo and SB 234551, a selective ETA antagonist.

**Methods**

Adult male normotensive rats (Sprague Dawley:300-350 gm) were anesthetized with 1-2% isoflurane during intraluminal suture placement in the middle cerebral artery. Rats were then randomized to receive 23.5 hour i.v. infusion of either vehicle (PBS; n=9) or SB-234551 (3 ug/kg/min, n=10 and 10 ug/kg/min, n=10) starting 75 minutes post MCAO. At 24 hours post surgery, diffusion weighted imaging (DWI), T2, and Gd-enhanced imaging was performed using a 4.7T/40 cm BRUKER BIOSPEC imaging spectrometer. The acquisition parameters at this time point were optimized for DWI contrast (SE:TR/TE=1,500/45 msec; 128X128; FOV=4X4 cm; slice thickness = 2mm; b factor = 1,550 sec/mm2) and T2 contrast (same parameters as DWI except TR/TE= 2,000/65 msec and diffusion gradients turned off). The Gd-enhanced gradient echo image acquisition parameters were optimized to generate one image per 1.5 sec (TR/TE=25/15msec, with a 0.2 ml bolus of Gd-DPTA (Berlex, NJ) at one slice selected by the DWI image. Blood gases and temperature were controlled within physiologic limits. Following MR imaging, the animals were sacrificed, the brains collected and subjected to histomorphometric evaluations using TTC staining.

**Image Analyses:** The perfusion delay index (PDI) was calculated from the 4 ipsilateral areas and their corresponding contralateral counterparts using the DWI image as a reference. Of these four areas, three were chosen in the cortical region and one in the striatal region. The PDI index was defined as a ratio of the mean signal intensity in the ipsilateral area to that in the contralateral counterpart and expressed as a percentage. This calculation was done only at that instance of time when the contrast uptake was maximal in the contralateral hemisphere. Analysis of variance was used followed by appropriate post-hoc comparisons with p<0.05 considered significant.

**Results**

A representative graph showing the perfusion delay index (PDI) at one cortical region is shown in Fig 1. In all the three cortical regions evaluated, we found significant differences between vehicle and 10 ug/kg/min SB-234551 group in the perfusion delay index (PDI). The 3 ug/kg/min group did not show a significant effect at any site. Moreover, neither dose had any significant effects on the striatum. The histological data confirmed the protective effects of SB-234551 by demonstrating statistically significant reductions in lesion sizes in both treatment groups (Fig. 2).

**Discussion**

The PDI index is heavily influenced by flow delays and its correlation with regional cerebral blood volume measurements needs to be further investigated. Use of Gd-enhanced MR imaging provides the opportunity to evaluate therapy with such in vivo perfusion indices in animal models of stroke. Region specific information demonstrated that the beneficial effects of SB 234551 were restricted to the cortex, where collateral flow is likely to be the greatest. This effect was also confirmed by region specific histomorphometric analyses. These data suggest that SB-234551 provides significant neuroprotective effects by possibly enhancing collateral flow.

**References**