Cleviprex Prevents Hippocampal Damage Following Severe Hypotension in Rats.

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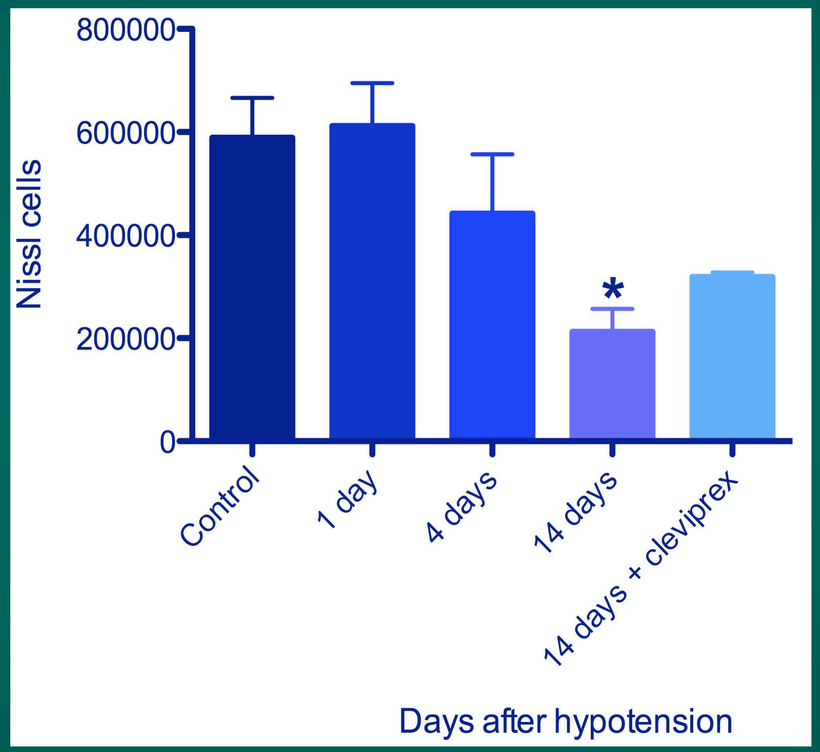
Introduction:

The aim of this study was to investigate whether clevidipine butyrate, an intravenous short acting dihydropyridine calcium channel antagonist (Cleviprex), has a neuroprotective effect in a rat hemorrhagic shock model of severe hypotension. Methods: 250g to 350g Sprague Dawley male rats were subjected to 3 separated episodes of 1 min of profound hypotension per hour for a total of 2 hours. Hypotension was induced by withdrawal of arterial blood from the right carotid artery, while under Isoflurane anesthesia. Mean arterial blood pressure was reduced 30 mm Hg for one min per hour, for a total of 3 minutes per rat. Shed blood was immediately reinfused in the venous circulation, returning systemic pressure to normal. Animals were divided into 5 groups: Group 1 was control (normal animals with no injury or treatment), Group 2 was euthanized at day 1 after the hypotensive injury, Group 3 was euthanized at day 4, Group 4 was euthanized 14 days after hypotension and group 5 was also euthanized 14 days after the hypotension, but was treated with clevidipine butyrate (Cleviprex) continuous intravenous (IV) infusion of 2 mg/kg for 30 min before and for 60 min after the insult. Animals were euthanized at the described time point and brains were collected for analysis. In order to generate an estimate of the number of surviving neurons in the CA1 hippocampal region, the number of Nissl cells were counted using the optical fractionator method of unbiased stereological cell counting techniques with a Nikon Eclipse 600 microscope and quantified using Stero Investigator software (MicroBrightField, Colchester, VT).

Figure 1. Estimated Total Number of Nissl Cells.



Cleviprex provided a neuroprotective effect in this model of brief, profound, repetitive hypotension

Introduction (continuation).

Statistical analysis was performed using a two-tailed unpaired t-test at a 95% confidence interval, after ANOVA, by comparing to the control group. Results: Brief, profound and repetitive hypotension results in progressive cellular loss in the hippocampal CA1 area, which reaches significance 14 days after the injury. Rats who had received Clevidipine did not suffer a significant reduction at 14 days.

Conclusion:

Cleviprex provided a neuroprotective effect in this model of brief, profound, repetitive hypotension. It is speculative that this may be mediated by its calcium blocker properties.

References:

1. Rubio A, Hakami L, Munch F, Tandler R, Harig F, Weyand M. Noninvasive control of adequate cerebral oxygenation during low-flow antegrade selective cerebral perfusion on adults and infants in the aortic arch surgery. J Card Surg 2008;23:474-9.

2. Moritz A, Koci G, Steinlechner B, Holzenbein T, Nasel C, Grubhofer G, Dworschak M. Contralateral stroke during carotid endarterectomy due to abnormalities in the circle of Willis. Wien Klin Wochenschr 2007;119:669- 73.

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