THE NOVEL 5-LIPOXYGENASE INHIBITOR (ABT - 761) ATTENUATES CEREBRAL VASOSPASM IN A RABBIT MODEL OF SUBARACHNOID HEMMORHAGE

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INTRODUCTION

- Leukotrienes and other eicosanoids, resulting from 5-lipoxygenase activity on arachidonic acid metabolism, have been implicated in the pathogenesis of cerebral VSP after SAH.

- 5-lipoxygenase activity enhanced after SAH. Significant in the pathogenesis of cerebral VSP? Inhibitor should ameliorate experimental VSP.
INTRODUCTION

- The present study evaluates the potential therapeutic value of ABT-761, a selective 5-lipoxygenase inhibitor on cerebral vasospasm in an in vivo rabbit model of SAH.
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METHODS

48 male rabbits (3-4 kg)  6 groups (n=8)

GROUP 1  SAH+P
GROUP 2  SAH+D20
GROUP 3  SAH+D30
GROUP 4  C+P
GROUP 5  C+D20
GROUP 6  C+D30
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METHODS

- Anesthetised  Intubated

- SAH - 5ml autologous blood into the cisterna magna

- Drug or placebo PO 30 minutes after hemorrhage and repeated 24 hours later.
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METHODS

- 48 hours after CSF was collected from the cisterna magna for ABT-761 concentration determination.

- Animals were sacrificed, using the perfusion-fixation method. Basilar artery was removed.

- The cross-sectional areas of basilar artery histological sections were measured by an investigator blinded to the treatment groups of the individual samples.
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**Statistical Analysis**

- A Kruskal-Wallis one-way analysis of variance was performed on the entire data set of morphometric measurements. Pairwise multiple comparisons *post-hoc* analysis was performed using the Bonferroni-Dunn method.

- Partial correlation coefficients were performed on CSF ABT-761 concentration values by treatment groups.
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RESULTS

- In placebo-treated animals, the average luminal cross-sectional area of the basilar artery was reduced by 68% after SAH compared to controls ($P<.0001$).

- After SAH the vasospastic response was attenuated in animals treated with 20 and 30 mg/kg representing a 28% and 35% reduction respectively ($P=.0011$ and $P=.0038$).
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DISCUSSION

- The greater degree of variability in drug concentration among control animals may indicate a trend towards variable drug utilization in the SAH animals than in Control animals.
DISCUSSION

- Vasospasm is a major complication after SAH

- Difficulties in prevention and treatment

- Pathogenesis still unclear, likely to be multifactorial, with inflammatory processes involved
DISCUSSION

- Leukotrienes are inflammatory mediators with cerebral vasoconstrictor properties
- Production is elevated in SAH
- CSF levels correlate with vasospasm
DISCUSSION

- ABT-761 is a second-generation, potent and selective inhibitor of leukotriene formation both in vivo and in vitro.

- Able to prevent experimental VSP, by attenuating the vascular effects of the 5-lipoxygenase products of arachidonic acid metabolism.
CONCLUSION

- Established the potential utility of a specific leukotriene inhibitor for the treatment of experimental VSP

- Indirect evidence for a role of inflammation in the pathogenesis of cerebral vasospasm

- Primate studies are needed to clarify whether 5-lipoxygenase inhibition has a potential role in the treatment of clinical cerebral vasospasm