Valproic acid in experimental and clinical SAH: Neuroprotective?

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Background

Subarachnoid hemorrhage (SAH) is associated with substantial morbidity and mortality. New treatments are needed. Valproic acid (VPA) is an antiepileptic drug with multiple mechanisms of action. Recent reports have suggested neuroprotective properties of VPA in ischemic stroke and traumatic brain injury animal models. We have previously shown that VPA decreases the degree of histological brain injury in a mouse model of SAH. We hypothesized that VPA would improve neurobehavioral outcomes after experimental SAH. We also analyzed existing SAH clinical trial data to determine if any beneficial effect of VPA can be seen.

Methods

Methods: 50 mice were allocated to 4 groups: SAH (n=13), SAH + VPA treatment (n=13), Sham (n=12), and Sham + VPA treatment (n=12). SAH was induced in male C57Bl/6J mice using a pre-chiasmatic injection model [1], and administered intraperitoneal injections of 400mg/kg VPA or saline vehicle after the procedure, every 12 hours for the first 48 hours, followed by daily injections up to 7 days in a blinded manner (See Figure 1). Global neurobehavioral assessments were made at 24 hours and 48 hours using the modified Garcia score [2]. Spatial memory and anxiety were assessed using modified versions of the Morris water maze (days 3-7) and open field test (day 7), respectively [3,4].

Subarachnoid Hemorrhage Model

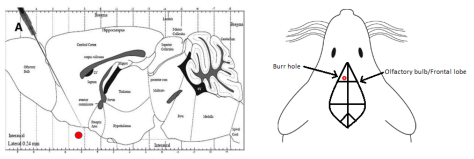

Figure 1: Anatomical landmarks relevant to the prechiasmatic injection mouse model of subarachnoid hemorrhage. Under orotracheal isoflurane anesthesia, 80 microL of litter-mate donor arterial blood was injected into the left prechiasmatic cistern via a 27G spinal needle.

To investigate the clinical effects of VPA in SAH, we used propensity score matching in patients enrolled in CONSCIOUS-1, a randomized controlled trial studying the effects of clazosentan on angiographic vasospasm after SAH [5,6]. The dichotomous outcome variables included the National Institutes of Health Stroke Scale (NIHSS, poor outcome defined as >= 10) at 6 weeks post-SAH, and the modified Rankin Scale (mRS, poor outcome defined as 4-6), extended Glasgow Outcome Score (GOSE, poor outcome defined as 1-4), and mini-mental status examination (MMSE, poor outcome defined as <= 24) at 12 weeks post-SAH.

Results

There was an overall 12% mortality (2 SAH, 1 SAH+VPA). Compared with sham mice, SAH mice demonstrated significantly worse acute neurobehavioral scores (ANOVA, $p<0.05$) and impaired spatial memory (ANOVA, $p<0.05$), which were both improved with VPA treatment (See Figure 2). Swim speed and escape latency were not significantly different among the 4 groups in the acquisition trials. Anxiety assessments were not significantly affected by SAH or VPA.

Neurobehavioral Assessments

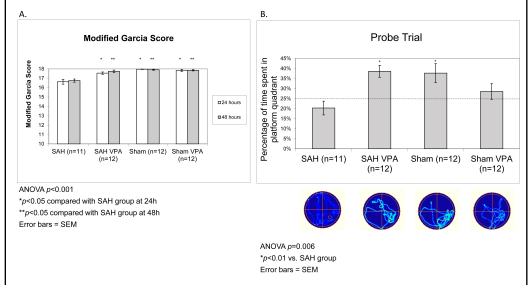

Figure 2. A) Modified Garcia Score assessed at 24 and 48 hours post-SAH. B) Morris Water Maze (MWM) probe trial results at day 7.

In the CONSCIOUS-1 clinical trial, 5% of patients were administered VPA. When compared to control SAH patients with similar covariate status (n=19-20), the CONSCIOUS-1 data suggests that SAH patients treated with VPA (n=18) may have had increased risk of poor outcome based on the mRS (p=0.051) and GOSE (p=0.004), but had no effect on the risk of death, or poor outcome on NIHSS or MMSE (See Table 1).

Outcome	ATT	n (VPA)	n (Control)	p value
Death	0.000	18	20	1.000
mRS	0.278	18	20	0.051
GOSE	0.444	18	20	0.004
NIHSS	0.111	18	20	0.300
MMSE	0.036	18	19	0.760

Table 1: Propensity-Score Analysis of SAH patients treated with VPA. ATT=Average treatment effect of the treated. ATT>0 implies increased risk of poor outcome.

Conclusions

VPA improves neurological outcomes in a mouse model of SAH. However, its benefits does not appear to translate into clinical SAH based on post-hoc analysis of clinical trial data. Further studies are needed before VPA can be used routinely in SAH aside from seizure treatment and prophylaxis.

Acknowledgements

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NREF Neurosurgery Research & Education Foundation
Government of Canada / Gouvernement du Canada
Vanier Canada Graduate Scholarships / Bourses d'études supérieures du Canada Vanier
Canada

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