

Serial CSF Sampling over a Period of 30 Hours via an indwelling Spinal Catheter in Healthy Volunteers: Safety, Tolerability and Measured Acetylcholine Profile

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PURPOSE

- Timed interval CSF sampling by indwelling catheterization can be a valuable corroborative tool for PK and PD assessment of drugs.
- CSF sampling in studies with drug candidates for Alzheimer's Disease have been conducted with the evaluating biomarkers acetylcholine, tau proteins, amyloid precursor protein (APP) and beta-amyloid fragments.
- The purpose of this study is primarily to study the feasibility and especially the safety and the burden for the healthy volunteers of serial CSF sampling within the CRO environment in order to establish a standardized research tool for future drug development studies.

METHODS

- This study is a validation study in healthy subjects.
- Eight (8) healthy male subjects with age between 55 and 75 were included in the study.
- After assessing eligibility the subjects entered the clinical pharmacology unit 2 days before starting the CSF sampling procedure.
- Hydration by drip infusion of 2L saline was performed for 24 h before starting the CSF sampling procedure.
- For antithrombotic purposes Fraxiparine (nadroparine calcium) was given 12 h and 36 h after intradural catheterization.
- CSF catheterization (Braun Spinocat[®]) was performed by a board certified anesthesiologist and CSF sampling by the investigator under aseptic conditions
- Subjects could freely move during the sampling period but were required to stay in a horizontally position for at least 24 hours after removal of the catheter.
- CSF and blood samples were collected from the healthy volunteers by interval sampling over a 30 hour period.
- Questionnaires for subject experience were performed regularly
- ACh was measured. Aβ-fragments, Tau, pTau and APP analysis is in preparation.

DEMOGRAPHICS

	Age (yr)	BMI (kg/m ²)	Height (cm)	Weight (kg)
Average	63.3	24.0	181.5	78.9
SD	5.0	2.0	9.4	8.3
min	57	20.5	169.0	66.1
max	69	26.3	194.0	92.8

RESULTS

ADVERSE EVENTS

Subjects:	N
Included in study	8
Completed study*	7
Completed study and reported AEs	6

AEs of 6 subjects:	N
Reported	25
Related	13
Possibly related	9
Very likely related	4

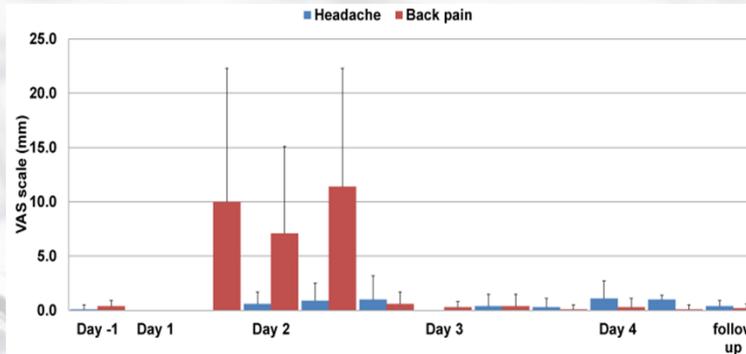
All AEs reported were mild and recovered during clinic stay. Paracetamol was given if required

*One subject was excluded because sampling was not successful

List of related AEs of 6 subjects:

Nausea
Headache
Light headedness
Sensation of pressure "behind eyes"
Dizziness
Muscle pain (lower back)
Neck pain
Back pain
Catheter site pain
Back discomfort
Tenderness i.t. catheter insertion site

VAS SCALES HEADACHE & BACK PAIN

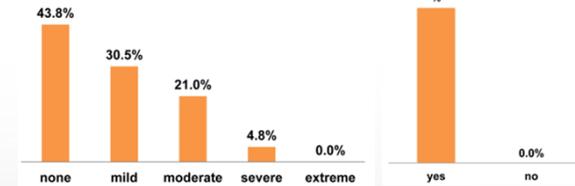


All subjects (N=7) were interviewed with VAS scales (ranging from 0-100 mm) concerning headache and back pain on Day -1 (1x), Day 1 (2x), Day 2 (3x), Day 3 (3x), Day 4 (2x) and follow up visit (1x) (error bars are S.D.)

CONCLUSION

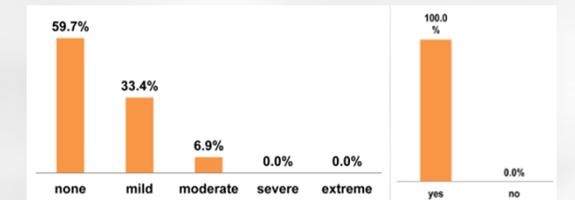
- The procedures needed for serial sampling of CSF for 30 h were well tolerated by all healthy volunteers.
- Bioanalysis of ACh in CSF shows acceptable inter-individual variability.
- Serial CSF sampling is a sophisticated tool for drug development.

SUBJECT QUESTIONNAIRES



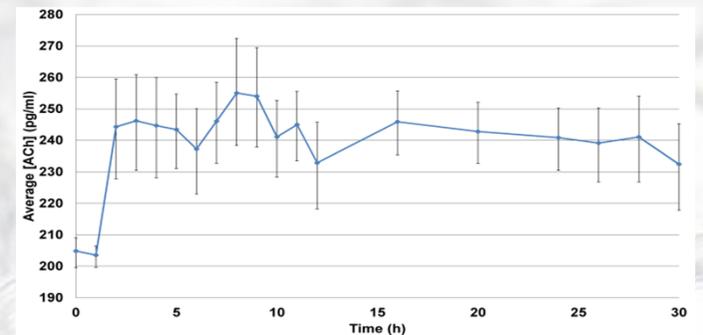
"Overall, how would you rate your experience of the insertion of the spinal tube?"

(average of 3 times asked during stay in clinic; N=7)



"Overall, how would you rate your experience of pain and/or discomfort?" (average of 7 times asked during post CSF sampling recovery period stay in clinic; N=7)

ANALYSIS OF ACH IN CSF



Average acetylcholine concentration (pg/ml) time plots (h) in CSF of 7 healthy volunteers (error bars are S.E.M.; CV% t=1&2 h is <3.9%;5.4%>, CV% t=3-30 h is <10.1%;16.7%>).

"Would you do the insertion of the spinal tube again?"

(average of 3 times asked during stay in clinic)

"Would you do the whole procedure again?"

(average in % of 4 times asked during stay in clinic; N=7)