Retrospective review of safety and tolerability of continuous cerebrospinal fluid (CSF) collections during Phase 1 studies in healthy volunteers and patients

B.A. English[1,2], H. Gevorkyan[3], D. Han[3], L. Gertsik[3], M. Avakian[1], J. Pauly[1], S. Jhee[1], L. Ereshefsky[1,4]

[1]PAREXEL International, Glendale, CA.; [2]Department of Pharmacology, Vanderbilt University Medical Center, Nashville, TN; [3]California Clinical Trials Medical Group, Glendale, CA.; [4]University of Texas, College of Pharmacy, Austin, TX.

Background

Methodologic question being addressed: Evaluation of safety and tolerability during continuous CSF sampling procedures in healthy volunteers and patients. This evaluation reports our more recent experience, and updates prior publications and presentations.

Introduction: Sampling of cerebrospinal fluid (CSF) has become an increasingly common procedure as part of a Phase 1 (Ph1) clinical development program in order to estimate CNS penetration, and to characterize pharmacokinetic (PK) and pharmacodynamic (PD) relationships related to dosing, allowing for correlations between peripheral and central compartments. Continuous CSF sampling via an indwelling catheter has been used by CCTMG/PAREXEL since the mid 1980's (Dynabridging studies[SM]) to measure drug concentration and changes in PD biomarker targets in healthy volunteers (HNVs), healthy elderly (HNEs) and in patients (ie. Alzheimer's disease). These studies provides central PK/PD time courses and permits comparison with peripheral PK/PD measures that can be explored across a range of doses, informing optimal dose strategies for future efficacy studies.

Continuous CSF studies up to 48 hours of collection can be repeated twice within the same subject with good safety and tolerability, provided sufficient time between lumbar catheterization. Serial CSF sampling has been conducted in both HNVs and in patients resulting in minimal adverse events.[1,2] As demonstrated in this poster our adverse event (AE) profile is at the lower end of the reported risk incidence for this procedure, as a result of experience and evolving technique..

The risks involved in conducting continuous CSF studies have been reported to be similar to those of single lumbar puncture which include post-dural puncture headache (PDPH), backache, infection and rarely nerve root damage, epidural or subdural bleeding.[1-4] Postural headache is the most common complaint and often resolves with bedrest, hydration and administration of oral analgesics. Estimates of PDPH associated with procedures such as continuous spinal anesthesia can be as high as 30%.5 In one study conducted in healthy subjects examining the two-small gauge spinal needles, revealed an usually high incidence of PDPH (78%).[5] Patient specific factors such as age, gender and technique specific factors such as needle size and type can influence risk of PDPH.[5] In this study, we evaluated the adverse event (AE) profile of our continuous CSF procedure in both healthy volunteers and in patients diagnosed with either a psychiatric or neurologic disorder.

CSF Procedure

• Healthy volunteer subjects OR patients underwent either single or repeated continuous CSF collection periods consisting of 6-14 sampling time points over 24-48 hours depending upon the specific study the subject participated.

•Subjects underwent spinal catheterization at the lumbar region (L3-L5) by a trained anesthesiologist using an continuous epidural tray (Smiths Medical, 4935MG) 17G or 20/22G Tuohy needle.

•Can obtain 5-10 ml of CSF per sample (0.5 ml/min).

•For subjects undergoing a repeat continuous CSF catheterization, a 14 day recovery period was instituted to avoid risk of increased AEs..

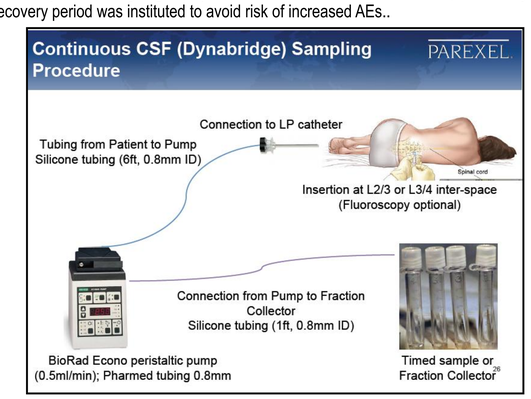

Fig 1: Continuous CSF sampling procedure. The spinal catheter inserted at L2/L5 is then connected to silicone (or alternate) tubing and to the peristaltic pump where serial samples are then collected and processed.

Methods

Retrospective chart review of all subjects who underwent continuous CSF collection procedures while participating in a Phase 1 clinical study program. Subjects consisted of young HNVs, elderly HNEs, and patients diagnosed with either Alzheimer's disease, Parkinson's disease, anxiety or major depression. Subjects underwent 1 to 2 continuous CSF sampling periods depending on study design. A continuous CSF sampling study consisted of either serial CSF collections of 6.0 cc of CSF, at a flow rate of 0.5 cc/min, collected over 26-36 hours, or the use of a fractional collection system. Typical CSF volumes are approximately 100 cc/24 hours. Variables such as subject demographics, health status, number of continuous CSF procedures and time interval between continuous CSF collections were compared to AE type and severity.

Results

Table 1*: Subject Demographics.*

Group	Total	M (%)	F (%)	# CSF collections	Duration of sampling (hrs)
HNVs (18-55)	149	128 (86)	21 (14)	1-2	26-36
HNEs (56>)	17	13 (76)	4 (24)	1-2	26-36
MDD	16	7 (44)	9 (56)	2	36
PD	18	13 (72)	5 (28)	1	26
AD (previous)[a]	63	44 (70)	19 (30)	1	24
MDD (previous)[b]	30	20 (67)	10 (33)	n/a	n/a

a. Data from Jhee SS et al., *Clin Res & Reg Affairs*. 2003;20(3):357-363.
b. Data from Ereshefsky L et al., ISCTM Fall Annual Meeting 2011.

Table 2*: Incidence of adverse events related to continuous CSF sampling.*

Adverse event	Overall incidence	Incidence, male (%)	Incidence, female (%)	Incidence, HNV (%)	Incidence, HNE (%)	Incidence, MDD (%)	Incidence, PD (%)	Incidence HNE (%)[a]
PDPH	57 (27)	34 (21)	23 (59)	26 (17)	9 (53)	20 (69)	8 (38)	10 (67)
Back pain	29 (14)	14 (9)	15 (38)	16 (11)	2 (12)	14 (48)	1 (5)	5 (33)
Neck pain	4 (2)	4 (2)	0 (0)	2 (1)	1 (6)	0 (0)	1 (5)	3 (20)
Nausea/vomiting	12 (6)	6 (4)	6 (15)	5 (3)	2 (12)	3 (10)	2 (9)	0 (0)
Dizziness	6 (3)	4 (2)	2 (5)	6 (4)	0 (0)	3 (10)	0 (0)	2 (13)
Lower extremity pain	14 (7)	4 (2)	10 (26)	8 (5)	1 (6)	6 (21)	0 (0)	0 (0)
Other	13 (6)	8 (5)	5 (13)	6 (4)	2 (12)	3 (10)	1 (5)	1 (3)
No AE reported	116 (54)	104 (65)	12 (31)	99 (66)	8 (47)	6 (21)	9 (43)	5 (33)

a. Data from previous HNV cohort (n=15) undergoing continuous CSF sampling using a 22G Spinocath needle.

1. Majority of subjects report no adverse events associated with the procedure, with PDPH and back pain representing the most frequent AEs reported overall (**Table 2**).
2. Overall incidence of reported AEs was higher in females and healthy elderly subjects, and MDD patients (**Table 2**).
3. AE rate among HNVs declined compared to earlier studies.

Table 3*: Impact of CSF spinal needle gauge on adverse events.*

Adverse event	17G (%)	20/22G (%)
PDPH	61 (35)	2 (5)
Back pain	30 (17)	3 (8)
Neck pain	4 (2)	0 (0)
Nausea/vomiting	10 (6)	0 (0)
Dizziness	5 (3)	0 (0)
Lower extremity pain	15 (9)	0 (0)
Other	12 (7)	1 (3)
No AE reported	88 (51)	34 (85)
# of blood patches	37 (21)	0 (0)

1. Use of a larger CSF spinal needle gauge (17G) was associated with a higher incidence of AEs and blood patch treatment (**Table 3**).

Results (continued)

Table 4*: Impact of total CSF volume (ml) on adverse events.*

Adverse event	<100ml (%)	>100ml (%)
PDPH	29 (23)	32 (67)
Back pain	9 (7)	21 (44)
Neck pain	4 (3)	0 (0)
Nausea/vomiting	4 (3)	6 (13)
Dizziness	4 (3)	2 (4)
Lower extremity pain	5 (4)	10 (21)
Other	5 (4)	7 (15)
No AE reported	75 (60)	12 (25)
# of blood patches	21 (17)	16 (33)

1. Collection of larger CSF volumes was associated with an increased incidence of AEs and blood patch treatment (**Table 4**).

Table 5*: Impact of # of CSF sample procedures on adverse events.*[a]

Adverse event	1 (%)	2 (%)
PDPH	27 (26)	36 (33)
Back pain	12 (12)	21 (19)
Neck pain	4 (4)	0 (0)
Nausea/vomiting	8 (8)	4 (4)
Dizziness	2 (2)	1 (1)
Lower extremity pain	4 (4)	11 (10)
Other	7 (7)	6 (6)
No AE reported	58 (56)	64 (59)
# of blood patches	5 (5)	18 (17)

a. Subjects either received 1 continuous CSF sampling period (24-36 hrs) or underwent 2 CSF sampling procedures separated by 10-14 days .

1. The number of CSF sample periods (1 vs 2) was not associated with an increased incidence of AEs. (**Table 5**).
2. Subjects and Patients undergoing 2 CSF sampling periods separated by either 10-14 days had a higher number of blood patches (**Table 5**).

Table 6*: Impact of CSF spinal needle gauge on subjects undergoing 2 continuous CSF sampling periods.*

Adverse event	17G (%)	20/22G (%)
PDPH	34 (49)	4 (10)
Back pain	18 (26)	3 (8)
Neck pain	0 (0)	0 (0)
Nausea/vomiting	4 (6)	0 (0)
Dizziness	1 (1)	1 (3)
Lower extremity pain	11 (16)	0 (0)
Other	5 (7)	1 (3)
No AE reported	30 (43)	34 (85)
# of blood patches	18 (26)	4 (10)

1. For subjects undergoing 2 CSF sampling periods, use of smaller CSF spinal needle gauge (20/22G) was associated with an overall few number of AEs and blood patches. (**Table 6**).

Table 7*: Impact of CSF sampling time intervals (26 vs 36 hrs) on adverse events.*

Adverse event	26 hrs (%)	36 hrs (%)
PDPH	31 (53)	51 (48)
Back pain	10 (17)	18 (17)
Neck pain	1 (2)	5 (5)
Nausea/vomiting	5 (8)	7 (7)
Dizziness	1 (2)	4 (4)
Lower extremity pain	2 (3)	9 (8)
Other	6 (10)	8 (8)
No AE reported	24 (41)	31 (29)
# of blood patches	12 (20)	23 (22)

1. Continuous CSF sampling time intervals (26 vs 36 hrs) was not associated with an an increased incidence of AEs. (**Table 7**).

Summary

1. Continuous CSF sampling studies in healthy, young normal volunteers is well tolerated.
2. Female healthy volunteers, healthy elderly and patients with MDD report a higher number of AEs associated with CSF sampling.
3. Larger CSF spinal needles and increased CSF sample volumes removed were associated with an overall increase in AEs.
4. The number of CSF sampling periods (1 vs 2) was associated with a slightly higher incidence of AEs, however use of smaller spinal needle gague (20/22G) resulted in fewer AEs.
5. CSF sampling windows of 26 or 36 hrs was equally tolerated among subjects and patients.
6. Small sample sizes in the HNE and patient studies make true AE estimates difficult when comparing to HNVs.

Conclusions

1. Continuous CSF sampling studies are generally well tolerated, with no reports of serious adverse events (SAEs) such as infection or nerve damage.
2. AE rates have declined over the more than two decades of sampling
3. Most common AEs reported are PDPH and back pain.
4. Some patient groups may report an increased frequency of AEs such as PDPH and require blood patches to alleviate symptoms.
5. Our results are consistent with previous studies that smaller CSF spinal needle size and smaller CSF sampling volumes are associated with fewer reported AEs and need for blood patches.[1, 2, 3]

References

1. den Daas I, Wemer J, Farha KA, et al., Serial CSF sampling over a period of 30 h via an indwelling spinal catheter in healthy volunteers: headache, backpain, tolerability and measured acetylcholine profile. *Eur J Clin Pharmacol*. 2013;69:1083-90.
2. Ereshefsky L, Jhee SS, Yen, M, et al., Cerebrospinal fluid beta-amyloid and dynabridging in Alzheimer's disease procedure development. *Biomark Med*. 2008;3(6):711-21
3. Jhee SS, Zarotsky V. Safety and tolerability of serial cerebrospinal fluid (CSF) collections during pharmacokinetic/pharmacodynamic studies: 5 years experience. *Clin Res Regulatory Affairs*. 2003;20(3):357-36.
4. Bruce JN Oldfield EH. Method for sequential sampling of cerebrospinal fluid in humans. *Neurosurgery*. 1988;23(6):788-90.
5. Gosch UW, et al., Post-dural puncture headache in youn adults: comparison of two small-gauge spinal catheters with different needle design. *Br J Anesth*. 2005;94(5):657-61.

Contact Information and Disclosures

Contact Information:
Brett A. English, PharmD, PhD or Hakop Gevorkyan, MD, MBA
PAREXEL International
1560 E. Chevy Chase Drive
Suite, 130
Glendale, CA. 91206
E-mail: brett.english@parexel.com
hakop.gevorkyan@cctrials.com

Disclosures: BAE, MA, JP, SSJ and LE are fulltime employees of PAREXEL International that receives financial compensation from numerous pharmaceutical companies for the conduction of clinical trials. HG, DH and LG are fulltime employees of the California Clinical Trials Medical Group (CCTMG) and serve as Principle Investigators on industry-sponsored clinical trials at PAREXEL.