Optimizing the Assessment of CNS Side Effects of a Novel Neuropathic Pain Compound

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Abstract

Background: The current study explored standardized psychometric tests to determine their ability to efficiently and sensitively detect common CNS side effects (dizziness, somnolence, sedation, and difficulties in concentration / attention) of a potent and specific novel neuropathic pain compound.

Methods: Forty-eight healthy volunteers were administered a battery of standardized tests as part of a randomized, double-blind, placebo-controlled, sequential, escalating study. This battery encompassed tests such as the Critical Flicker Fusion (CFF) Test, the Continuous Performance Test-Identical Pairs (CPT-IP), the Digit Symbol Substitution Test (DSST), the Line Analogue Rating Scale (LARS), and the Epworth Sleepiness Scale (ESS), known to be sensitive to the side-effects of similar drugs such as pregabalin/gabapentin.

Results: Descriptive statistics suggested overall good psychometric properties. Variables were highly inter-correlated, and most correlations with d prime and reaction time measures were with the 2 digit CPT-IP. In an effort to further assess this and control Type 1 error, a factor analysis was conducted. A two factor varimax rotated model best explained the data with factors corresponding to complex attention (d primes for 2 and 4 digit CPT-IP values were.68 and .59, respectively) and processing speed (reaction times for 2 and 4 digit CPT-IP and DSST values were .62, .79 ,and -.47, respectively). Cronbach's alphas (0.51, 0.57) suggest that these factors are internally consistent and assess common underlying constructs.

Conclusions: This data will be utilized to form weighted summary composite measures to assess dose related changes permitting more appropriate and powerful comparisons than is typically afforded by descriptive statistics.

Background

- This study was designed primarily to assess the CNS side effects of a pregabalin-like compound intended for eventual use in neuropathic pain.
- According to the pregabalin prescribing information, the most common adverse reactions (≥ 5% and twice placebo occurrence) are dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and abnormal thinking (primarily difficulty with concentration / attention).
- Therefore, measures and scales were selected that were known to be sensitive to pregabalin side effects such as:

Sedation	Line Analog Rating Scale (LARS) – total score
Sleepiness	Epworth Sleepiness Scale (ESS) - total score
Psychomotor Speed	Digit Symbol Substitution Test (DSST) – total number of correct digits in 90 seconds
Attention / Working Memory	Continuous Performance Test, Identical Pairs version (CPT-IP) – d prime and reaction time (mean and standard deviation) for both the 2-digit condition and the 4-digit condition
Information Processing Capacity	Critical Flicker Fusion (CFF) Test – threshold critical flicker fusion frequency
Dizziness	Vertigo Symptom Scale - Short Form (VSS-SF) – total score and vertigo-balance subscore
Ataxia	Brief Ataxia Rating Scale – total score

Methods

- This was a randomized, double-blind, placebo-controlled, sequential, escalating, single dose study of 48 normal healthy volunteers (45 men / 3 women) conducted at Worldwide Clinical Trials - Drug Delivery Solutions' (WCT-DDS) inpatient treatment facility in San Antonio, TX.
- There were six single dose cohorts of 8 subjects (randomized in a 3:1 ratio [verum: placebo]). A total of 36 subjects received verum and 12 subjects received placebo.
- Subjects were admitted to the clinical pharmacology unit on Day -2 in sequential cohorts. On Day 1, subjects received a single oral dose of verum or placebo, followed by serial blood and urine collection through 72 hours post dose to assess pharmacokinetics (PK).
- In addition, safety and pharmacodynamic (PD) assessments were conducted periodically post dose.
- Doses were sequential up to the point of intolerability followed by a final lower dose cohort in an effort to identify a maximally tolerated dose (MTD).

Summary of Demographics at Baseline

Parameter	Statistic	Cohort 1 (N=6)	Cohort 2 (N=6)	Cohort 3 (N=6)	Cohort 4 (N=6)	Cohort 5 (N=6)	Cohort 6 (N=6)	Placebo Total (N=12)	Overall (N=48)
Age (years)	Mean	27.2	31.7	33.5	29.3	35.2	32.3	31.1	31.4
	Std. Dev.	5.46	5.79	7.31	6.95	8.93	9.27	5.53	6.91
Gender									
Male	N (%)	6 (100.0)	6 (100.0)	5 (83.3)	6 (100.0)	6 (100.0)	4 (66.7)	12 (100.0)	45 (93.8)
Female	N (%)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	3 (6.3)
BMI (kg/m^2)	Mean	26.5	24.5	25.7	24.6	25.6	25.3	23.7	24.9
	Std. Dev.	3.74	1.88	3.06	3.52	1.70	2.82	2.08	2.68
Ethnicity									
Hispanic or Latino	N (%)	1 (16.7)	3 (50.0)	3 (50.0)	0 (0.0)	2 (33.3)	4 (66.7)	3 (25.0)	16 (33.3)
Other	N (%)	5 (83.3)	3 (50.0)	3 (50.0)	6 (100.0)	4 (66.7)	2 (33.3)	9 (75.0)	32 (66.7)

Summary of Pharmacodynamic Measures at Baseline

Variable	Mean	Std Dev
Lars	42.64	13.20
Cffmean	38.63	3.31
Dprime2	3.69	0.91
Rxtime2	451.37	81.43
Dprime4	1.93	0.99
Rxtime4	519.37	82.59
ESS	6.10	3.33
DSST	61.83	8.81

	cffmean	dprime2	rxtime2	dprime4	rxtime4	ESS	DSST
lars4	0.06914 0.6405	0.11183 0.4492	-0.11076 0.4536	-0.04422 0.7654	-0.34965 0.0148	0.22727 0.1203	-0.08659 0.5584
cffmean		0.39957 0.0049	0.15668 0.2876	0.08791 0.5524	0.17052 0.2466	-0.09858 0.5050	0.10561 0.4750
dprime2			0.49500 0.0003	0.33893 0.0184	0.44538 0.0015	-0.29538 0.0415	-0.12845 0.3843
rxtime2				0.22965 0.1164	0.67055 <.0001	-0.27743 0.0562	-0.28542 0.0492
dprime4					-0.04524 0.7601	-0.28946 0.0468	0.26740 0.0662
rxtime4						-0.23672 0.1052	-0.27531 0.0582
ESS							-0.00519 0.9721

Results

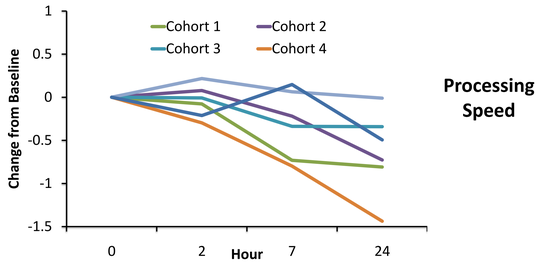
To control Type I error and reduce data, a series of factor analyses were conducted, and a two factor varimax rotation model proved to be the best fit with factors corresponding to complex attention and processing speed.

Results (cont.)

These factors were used to create weighted summary scales using z-transformations from baseline data. Each of these summary scales was then compared at 2, 7, and 24 hours post dose for each of the six cohorts.

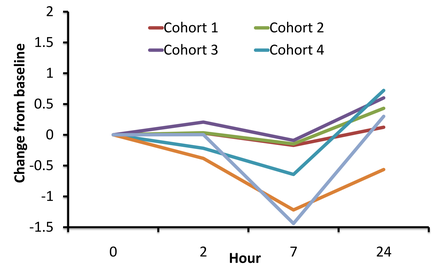
Variable	Factor 1 Complex Attention	Factor 2 Processing Speed
1. Lars4	-4	-24
2. Cffmean	38	4
3. Dprime2	68 *	29
4. Rxtime2	48	62 *
5. Dprime4	59 *	-21
6. Rxtime4	30	79 *
7. ESS	-42 *	-15
8. DSST	15	-47 *
Cronbach's alpha	0.51	0.57

A profile analysis was conducted to determine if the profile shape of these two summary scales differed from each other and from zero for each of the six cohorts (cohort by time interaction p>.05).



Processing Speed

Complex Attention



Conclusions

- There were no unusual or unexpected adverse events (AEs) related to the study medication.
- Verum was well tolerated at low doses with primary treatment emergent adverse events (TEAEs) seen in areas reflecting the mechanism of action, including dizziness and sedation.
- The numerous psychometric tests and scales demonstrated varying degrees of correlation with AE reports, but none appeared to detect symptoms with greater sensitivity than these reports.
- However, weighted summary scales based on a priori factor analyses were able to effectively profile dose-related declines in both complex attention and processing speed at various time points to help establish the MTD .

No conflicts of interest exist in the research and development of this poster