A randomized, double-blind, placebo-controlled, single dose, 3-way cross-over study in healthy elderly subjects to develop an anti-cholinergic pharmacological challenge with biperiden

C. Bakker[1], M.J. van Esdonk[1], M. de Kam[1], L.G.J.M. Borghans[1], F.E. Stuurman[1], G.J. Groeneveld[1]

[1]Centre for Human Drug Research, Leiden, the Netherlands

Introduction

Currently, several selective M_1 muscarinic acetylcholine receptor (M_1 mAChR) agonists are under development as symptomatic treatment for the cognitive effects of Alzheimer's disease. In early phase development of these drugs, usually performed in healthy subjects, it is difficult to demonstrate acute pharmacodynamic (PD) effects, e.g. on cognitive function, due to ceiling effects of the PD tests in healthy subjects. A challenge model affecting the mAChR that induces temporary reversible cognitive deficits could be used for proof-of-pharmacology of new M_1 mAChR agonists. Biperiden is a selective M_1 mAChR antagonist that passes the BBB and therefore a suitable challenge. Investigating a biperiden challenge model with repeated PD and pharmacokinetic (PK) measurements in elderly subjects was not done before.

Aim

- To determine the profile of effects on the central nervous system at several time points after 2 mg and 4 mg biperiden in comparison to placebo.
- To determine the PK of biperiden
- To determine the plasma concentration-effect relationship of biperiden on NeuroCart tests using population PK-PD modeling.

Methods

In this 3-way cross-over study, biperiden (2 mg and 4 mg) and placebo were administered to 12 healthy elderly subjects (65-80 years, MMSE≥28). Pre-dose and post-dose PD was repeatedly assessed using the NeuroCart battery of tests including the adaptive tracking test (sustained attention), n-back test (working memory), eye movements (alertness), visual verbal learning test (VVLT) (immediate and delayed memory), tapping (motor speed), visual analogue scale (VAS) Bond and Lader (mood), VAS nausea, body sway (balance), pharmacological electroencephalography, the event related potential mismatch negativity, pupillometry (autonomic nerve system). PD results were analysed with a mixed model ANCOVA and compared with placebo. A PK-PD model was developed using non-linear mixed effect modelling .

Results

- Effects on tests of learning and memory.
  - The adaptive tracking performance (sustained attention) was consistently impaired (mean difference up to -2.095%, 95% CI [-3.043;-1.148], p=<0.001) (figure 1) after 2 mg and 4 mg biperiden.
  - The mean reaction time on the n-back test 0-back and 1-back condition increased up to 49.9 ms (95% CI [21.854; 77.882], p=0.0016) (figure 2) after 4 mg biperiden.
  - In the VVLT (memory), fewer words were recognised (mean difference -6.5, 95% CI [-10.8; -2.2], p=0.0053) or recalled (mean difference -3.1, 95% CI [-5.9; -0.2], p=0.0344) after 4 mg biperiden.
- PK showed high inter-occasion variability and high inter-subject variability (Table 1 and 2). PK data was best fit by a 2-compartment model with linear elimination. A lag time and transit compartment were required. No covariates were identified.
- PK/PD analysis showed direct linear drug effect on adaptive tracking (slope effect of -0.98 %/ng/L, RSE 12.34%) (figure 3), a sigmoid Emax drug effect on the reaction time in n-back 0-back condition (Hill coefficient of 2.25, RSE 18.87), and a linear drug effect on the reaction time in n-back 1-back condition (slope effect of 16.18 ms/ng/L, RSE 16.52%).

Conclusions

These results support the idea that this biperiden challenge model can be used for proof-of-pharmacology and that it is feasible in elderly subjects. The developed model can take into account the affinity of each compound to study the reversal of biperiden induced cognitive impairment, already in a phase 1 clinical trial. Additionally the model can be used to optimize the design of dosing times and sampling time points to reduce subject burden but increase the amount of information obtained.

Table 1: PK characteristics of biperiden. Non compartmental analysis.

	2 mg biperiden			4 mg biperiden		
	Mean	SD	CV	Mean	SD	CV
Cmax (ng/ml)	3.51	1.99	56.69	7.45	5.99	80.44
Term (h)	6.37	3.10	48.65	9.41	3.55	37.67
AUC_0_last (ng*h/ml)	18.35	10.77	58.68	39.47	23.79	60.27
Tmax (h) (min-max)	2 (1 - 4.02)			2 (1 - 4)		

Table 2: PK characteristics of biperiden after modeling

Parameter	Estimate (CV%)
Lag time (h)	0.54 (BOV = 67%)
Absorption rate constant (/h)	2.73 (BOV = 82%)
Volume of distribution - Central (L)	491.40 (IIV = 70%)
Volume of distribution - Peripheral (L)	1537.00
Inter-compartmental clearance (L/h)	79.03
Clearance (L/h)	78.06 (IIV = 117%, BOV = 10%)
Proportional residual error	0.03

BOV= between occasion variability; IIV= inter individual variability, CV = coefficient of variation

Figure 1: The adaptive tracking test (3-minute test for sustained attention) was performed repetitively after dose administration. Mean score per dose level was compared with placebo. This figure shows the change in tracking from baseline.

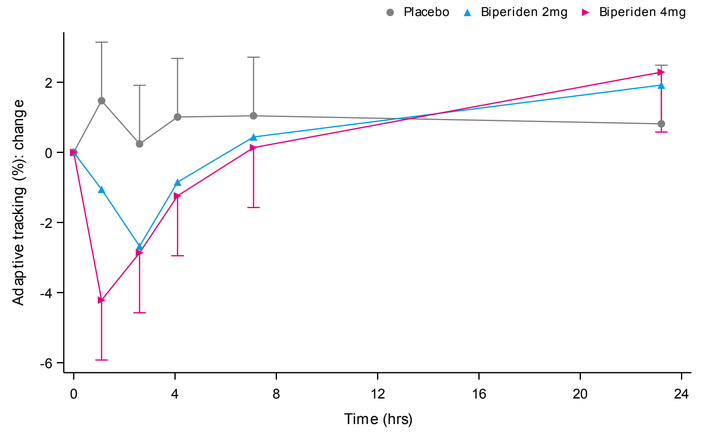


Figure 2: The n-back test (work memory) was performed repetitively after dose administraton. This figure shows the change in reaction time during the 1-back condition from baseline.

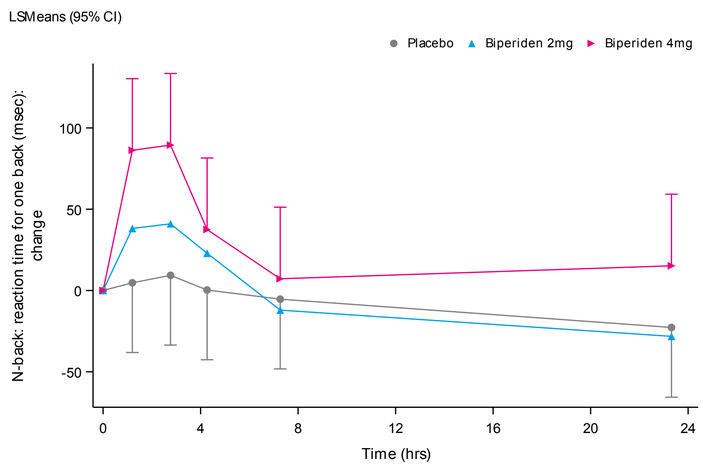
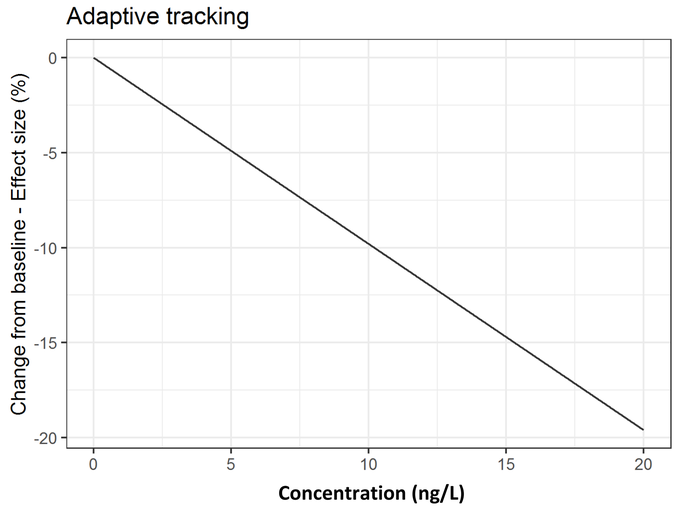


Figure 3: PK-PD analysis result: the linear effect of biperiden on the adaptive tracking test.



CHDR
Centre for Human Drug Research

Centre for Human Drug Research | Zernikedreef 8 | 2333 CL Leiden | The Netherlands | Tel +31 71 52 46 400 | info@chdr.nl | www.chdr.nl