THE ROLE OF P-GLYCOPROTEIN IN CENTRAL ANTIHISTAMINE EFFECTS

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Introduction

- Research in rodents suggests that the occurrence of sedative effects of antihistamines (AHs) partly depends on affinity for the P-glycoprotein (P-gp) drug efflux pump (Figure 1)[1,2].

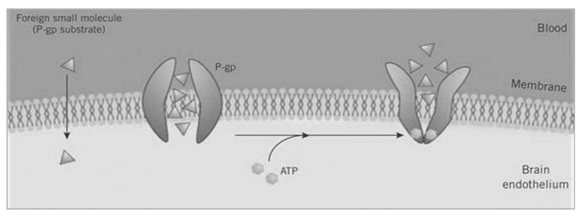


Figure 1 P-gp substrates (i.e. certain AHs) are pumped out of brain cells by the P-gp transporter. Therefore, less binding in the brain is possible, ensuring less sedative effects in the CNS (Adapted from [3]).

- Also, by blocking P-gp, a P-gp substrate (such as a non-sedating AH) is not pumped out of brain cells anymore.
  → Therefore more chance to bind at H1 receptors
  ➔ A normally non-sedative AH causes sedation.

- **Aim of this study**: Investigate whether combining the AH cetirizine (CET) with P-gp blocker verapamil (VER) increases sedation by means of impaired performance (i.e. increased reaction time) on attention, in humans.

Hypotheses:
- CET (P-gp substrate) → performance not affected
- CET + VER → performance impaired

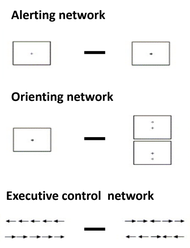
Design & Assessments

13 volunteers (6 women) participated in a placebo-controlled, randomized, double blind design. Cognitive performance was assessed using the Attention Network Test (ANT, Figure 2) in combination with fMRI. Additionally, blood samples were drawn to determine drug concentrations in plasma.

Treatments were as follows:

	Session 1	Session 2
Test day 1	Placebo	Verapamil 120 mg
Test day 2	Cetirizine 15 mg	Verapamil 120 mg (+ Cetirizine 15 mg)*

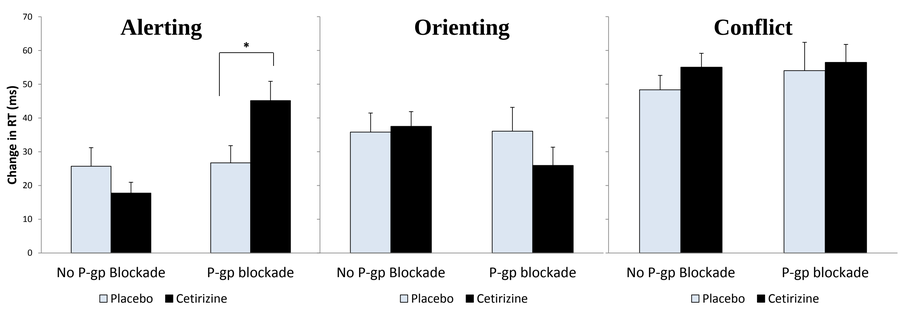
* Because of the relative long half-life (7 – 11 hours) of cetirizine, during this second session the combination of cetirizine 15 mg with verapamil 120 mg was measured.



- By combining warning cues and flankers, the ANT provides information about three separate attention networks.
- The no cue condition is the baseline. The center cue alerts, the double cue is involved in orienting, and incongruent flankers are involved in executive control.
- By subtracting the cues and flankers as shown in the left figure, the efficiency of the networks are measured[4].

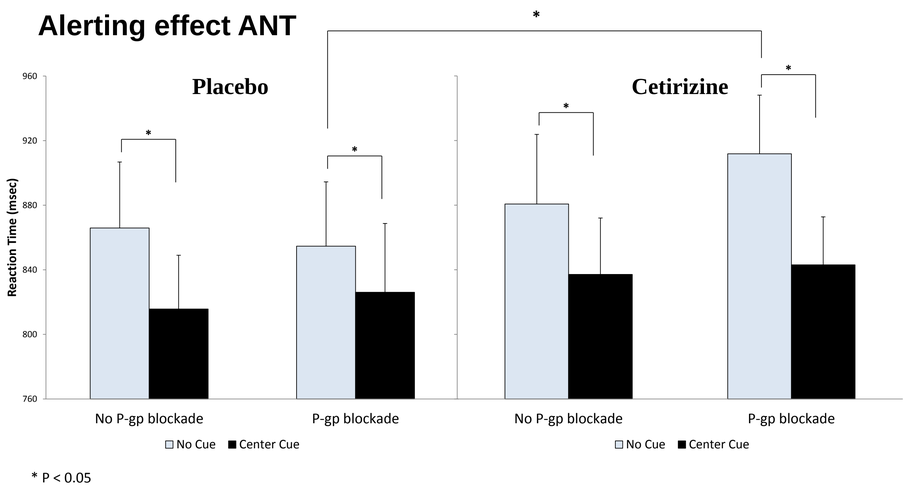
Results

Attention Network Test (ANT)



* P < 0.05

Blocking P-gp affected the alerting network (center cue minus no cue) significantly after CET intake compared with PLA. The other two attention networks measured with the ANT were not affected.



* P < 0.05

Combining CET with P-gp blocker VER increased reaction time mostly in the no cue condition and not in the (alerting) center cue condition. This indicates that even though CET does increase sedation after P-gp blockade compared with PLA, alerting is not affected.

Blood Samples

Treatment	No P-gp blockade Plasma concentration Mean ± SE		P-gp blockade (Verapamil) Plasma concentration Mean ± SE	
	CET (mg/l)	VER (mg/l)	CET (mg/l)	VER (mg/l)
CET	0.15 ± 0.03	0.00 ± 0.00	0.21 ± 0.01	0.08 ± 0.02
PLA	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.06 ± 0.02

Plasma concentrations (mg/l) confirm the presence of CET and VER in the expected conditions. The difference between CET with and without P-gp blockade was not significant.

Procedure & Statistics

Each test day lasted from morning until afternoon:

9:30	10:15	11:30	11:45	13:00	14:15	14:30	16:10
Arrival Drug screen Pregnancy test Questionnaires	Intake Pla/Cet	Blood sample	Tmax Cet Test session 1	Intake Ver	Blood sample	Tmax Ver* Test session 2	End of Testday

Data were analyzed by means of paired samples *t*-tests.

- Effects of CET 15 mg without p-gp blockade were compared with placebo (PLA).
- Effects of VER 120 mg were compared with VER + CET (during test session 2 VER was expected to interact with CET).

➔ This way, possible effects of VER alone were not taken into account.

Discussion

- The alerting effect is apparent in all treatment conditions, as reaction time (RT) decreased after a center cue, showing that the task was effective.
- Plasma concentrations indicate that the treatment manipulations were effective as well.

- RT was increased in the cue conditions of the alerting network (in the VER + CET condition) indicating that, as expected, P-gp is involved in the amount of sedation caused by antihistamines (which are P-gp substrates) in humans.

- However, RT in the center cue condition was not impaired, meaning that alerting was not affected.
  → Norepinephrine (NE) is known to influence alerting. Blocking the NE system blocks the effect of warning signals[5] (such as the center cue). As CET blocks the HA system, this might explain the lack of center cue effects.

Conclusion:
The present study indicates that P-gp is involved in central antihistamine effects in humans.

Literature

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For further information

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