THE ROLE OF P-GLYCOPEPTIDE 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)\(^1,2\).
- 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.

### Hypothesis:

- 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:**

- **Placebo**  
- **CET**  
- **CET + VER**

**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

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.

### Results

- **Attention Network Test (ANT)**
  - CET (P-gp substrate) ➔ performance not affected
  - CET + VER ➔ performance impaired

### Blood Samples

- **No P-gp Blockade**
  - CET + VER
- **P-gp Blockade (Verapamil)**
  - CET + VER

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.

### 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\(^3\) (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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