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Evaluation of Phenotyping by Multi-Drug Cocktail and Genotyping of the Human Cytochrome P450 Iso-enzymes CYP2D6, CYP2C19, CYP3A4 and CYP3A5 in Healthy Volunteers

I. Den Daas [1], J. Wieling [1], R. Schwietert [1], W. Tamminga [1], J. Wemer [1], J. Hempenius [2]
[1] QPS Netherlands BV, [2] QPS Holding LLC

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PURPOSE

- Cytochrome P450 (CYP) iso-enzymes are important for drug metabolism.
- Genetic polymorphisms have been identified for some of these enzymes, resulting in individuals with different metabolizing capacities (extensive metabolizers versus poor metabolizers).
- CYP enzyme activity can be evaluated by phenotypic screening using CYP specific substrates: measurements of the parent compound and its metabolite in plasma and/or urine.
- Drug cocktails can be used to test enzyme activity of different CYPs at once: reduction in time, costs and the number of subjects.

THE QPS COCKTAIL

QPS Netherlands B.V. has developed a multi-drug cocktail to assess the activity of 4 different CYPs: CYP2D6, CYP2C19, CYP3A4 and CYP3A5

OBJECTIVES

- To test whether there is a pharmacological interaction between the 3 CYP substrates dextromethorphan, omeprazole and alprazolam when administered in combination to healthy subjects.
- To optimize the administration regimen, allowing as few sampling points as possible.
- To evaluate safety and tolerability of the 3 CYP substrates when given in combination.

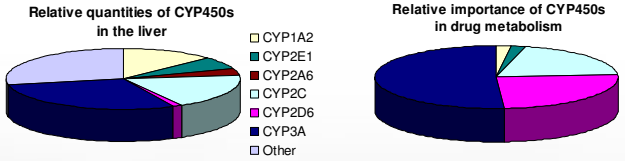
METHODS

- Randomized, single-center, open label, 4-period cross-over study in 12 healthy male volunteers.
- Drugs were administered per os, as a single dose or in combination, with a wash-out period of 7 days between treatments.
- Venous blood sampling at pre-dose, 1h, 2h, 3h, 4h, 6h and 8h, urine collection from 0-8h.

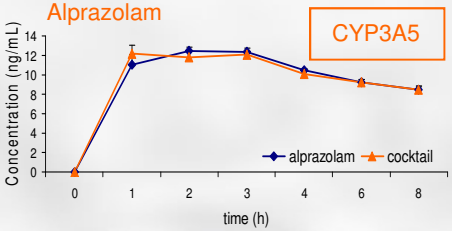
STUDY MEDICATION

Treatment	Metabolites	Iso-enzymes
A.dextromethorphan 30 mg *Touxium antitussivum®*	dextrorphan	CYP2D6
	3-methoxymorphinan	CYP3A4
B.omeprazole 20 mg *Losec® MUPS®*	5-hydroxy-omeprazole	CYP2C19
	omeprazole sulphone	CYP3A4
C.alprazolam 1 mg *Xanax®*	alpha-hydroxy-alprazolam	CYP3A5
D.combination of A, B and C		

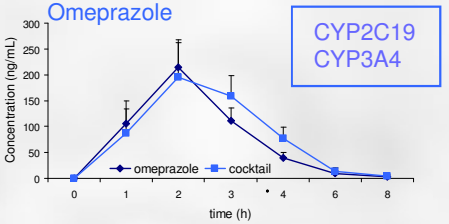
CYP450 DISTRIBUTION IN THE HUMAN LIVER



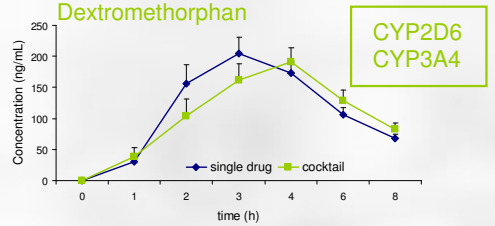
RESULTS



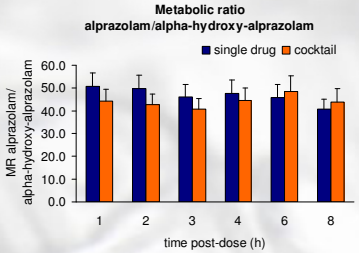
Concentration-time curve of alprazolam in plasma. The profile does not change when alprazolam is administered in a cocktail, compared to administration of the drug alone (data are presented as average +/- SEM).



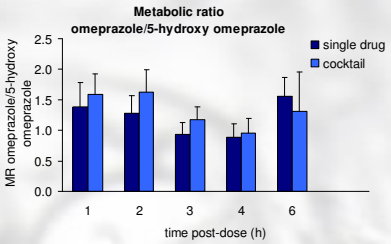
Concentration-time curve of omeprazole in plasma. There is no difference between the profile if omeprazole is administered alone or as part of a cocktail.



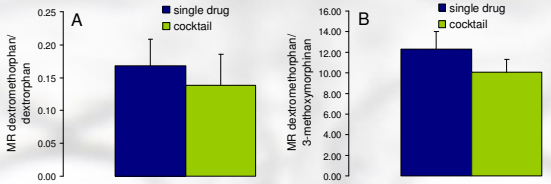
Concentration-time curve of dextrorphan, a metabolite of dextromethorphan (CYP2D6). Dextromethorphan could not be measured in plasma. Dextrorphan curves are similar between the cocktail and the single drug group.



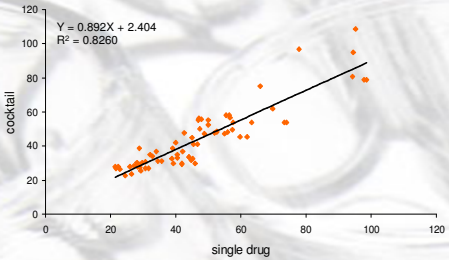
The metabolic ratio alprazolam/alpha-hydroxy-alprazolam (CYP3A5) remains constant for 8h post-dose and does not differ between single drug administration and cocktail.



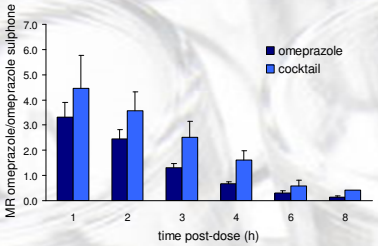
The metabolic ratio omeprazole/5-hydroxy-omeprazole (CYP2C19) does not change when omeprazole is given in a cocktail, compared to administration of the single drug.



The metabolic ratios dextromethorphan/dextrorphan (A, CYP2D6) and dextromethorphan/3-methoxymorphinan (B, CYP3A4), measured in urine, do not differ between single drug treatment and cocktail treatment.



Correlation between the metabolic ratio alprazolam/alpha-hydroxy-alprazolam (CYP3A5), when alprazolam was administered alone or in a cocktail. The slope is significantly different from 1 (P = 0.030), the intercept does not differ from 0 (P = 0.333).



The metabolic ratio omeprazole/ omeprazole sulphone (CYP3A4) decreases over time, but does not differ between treatments (single drug or cocktail).

Subject	CYP2D6 (*3)	CYP2D6 (*4)	CYP2C19 (*2)	CYP3A4 (*1B)	CYP3A4 (*3)	CYP3A5 (*3)	CYP3A5 (*6)
1	WT	WT	HE	WT	WT	HO	WT
2	WT	WT	HE	WT	WT	HO	WT
3	WT	WT	WT	WT	WT	HO	WT
4	WT	HE	HE	WT	HE	HO	WT
5	WT	HE	HE	WT	WT	HO	WT
6	WT	WT	HE	WT	WT	HE	WT
7	HE	WT	WT	WT	WT	HE	WT
8	WT	WT	WT	HO	WT	WT	HE
9	WT	WT	WT	WT	WT	HO	WT
10	WT	HE	WT	WT	WT	HO	WT
11	WT	HE	HE	WT	WT	HO	WT
12	WT	WT	WT	WT	WT	HO	WT

Genotypes: WT = wildtype, HE = heterozygote, HO = homozygote

CONCLUSIONS AND FUTURE DIRECTIVES

- There were no obvious pharmacological interactions between alprazolam, omeprazole and dextromethorphan, when administered in a cocktail.
- All drugs were well tolerated, both as a single administration and in a cocktail.
- Metabolic ratios for alprazolam and omeprazole showed the lowest variation between 2h and 4h post-dose. Dextromethorphan could only be measured in urine, not in plasma.
- Plasma alprazolam concentration remained high throughout the 8h PK sampling period, indicating that a lower dose of this drug might be preferred.
- In a next experiment, CYP-inhibiting or inducing factors could be used, in order to assess whether changes in CYP activity can be measured with the Xendo cocktail.