PharmaNeuroBoost

Low dose Pipamperone significantly binds 5-HT2A receptor without clinically relevant D2 receptor binding: a PET study

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Purpose of the study

Pipamperone (PIP) is a mild neuroleptic used at dosages ranging from 40 to 360 mg per day in a number of European countries. In a proof-of-concept study a low daily dose of PIP (5 mg b.i.d) was found to enhance the antidepressant effect of the selective serotonin re-uptake inhibitor citalopram at mean trough plasma concentrations of 13.8 ng/mL. This clinical effect has been related to a selective, significant 5-HT2A/D4 antagonism, without clinically relevant D2 receptor binding. In order to confirm this mode of action and to optimize dosing for subsequent studies, a PET (Positron Emission Tomography) study was performed.

Objectives of this study:

-Determine the relationship between PIP dose, PIP plasma concentration and 5-HT2A receptor occupancy (RO) to document to what extent relevant 5-HT2A binding occurs at dosages used in the POC study.

-Demonstrate a lack of clinically relevant binding of PIP to the D2 receptor at the dosages with a relevant 5-HT2A binding to prevent dopamine driven side effects and as such to obtain an optimal target binding range.

Methods

Ten healthy subjects received one of four different treatments with PIP; Two subjects received a single high dose of 120 mg PIP (A, to achieve near maximum binding), 3 subjects 10 mg PIP b.i.d. for 6.5 days (B), 3 subjects 15 mg PIP q.d. for 6.5 days (C) and 2 subjects a single dose of 30 mg PIP (D). Central nervous RO was assessed by means of Positron Emission Tomography (PET) using a dynamic scanning technique. In treatments A, B, and C the specific tracer 11C-MDL100907 was used to assess 5-HT2A RO (in combination with arterial input modeling). In treatment D 11C-raclopride was used to assess D2 RO (using the simplified reference tissue model). Three scans were made for each subject (including one baseline scan). Full pharmacokinetic (PK) profiles of PIP were determined in each subject. Prolactin was measured as an indirect measure of clinically relevant D2 binding.

PK/PD modeling was performed to obtain a relationship between PIP plasma concentrations and 5-HT2A RO (using the software NONMEM). RO was estimated by the sigmoidal model: 100% * C/(C+EC_{50}), with C the model estimated PIP plasma concentration at the mid time of PET assessment and EC_{50} the PIP concentration corresponding to 50% of the maximum binding.

D2 RO was plotted against the predicted PIP plasma concentration by the model. These concentration-RO relationships were compared to the effective concentrations obtained in the POC to obtain a target binding range.

Results

Table 1: PK parameters for PIP treatment A-D

PK of pipamperone	Treatment A (n=2) SD 120 mg	Treatment D (n=2) SD 30 mg (min-max)
C_{max}, ng/ml	152.0 ± 24.25	(24.4 – 24.5)
T_{max}, h	1.5 (1.0-1.5)	(3.0 – 6.0)
AUC_{∞}, ng.h/ml	1849 ± 158.6	(407.8* - 522.7*)
$t_{1/2term}$, h	15.64 ± 2.575	(12.31* - 21.45*)
PK of pipamperone	**Treatment B (n=3)** MD-6.5 days 10 mg b.i.d.	**Treatment C (n=3)** MD-6.5 days 15 mg q.d.
C_{min}, ng/ml	18.30 ± 6.497	9.773 ± 7.052
C_{max}, ng/ml	26.87 ± 9.843	20.97 ± 12.59
T_{max}, h	2.0 (2.0-4.0)	3.0 (3.0-7.0)
AUC_{τ}, ng.h/ml	271.7 ± 92.22	343.8 ± 216.5

** Accurate determination not possible. SD: single dose, MD: multiple dose. T = 12h for Treatment B and 24 h for Treatment C.*

Figure 1: No indication for hysteresis.
Observed and predicted plasma conc. of PIP and observed and predicted receptor occupancy of 5-HT2A of an individual subject after a single dose of 120 mg PIP.

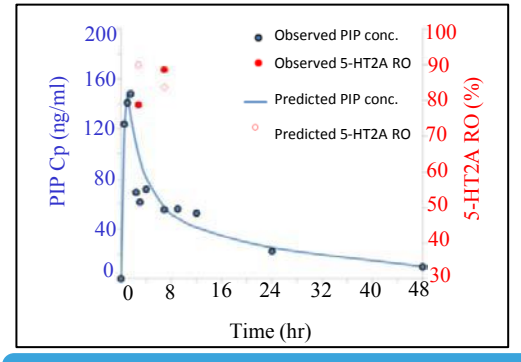


Figure 2: 5-HT2A RO ranged from 43.2% to 75.2% for the 10 mg PIP b.i.d. and 15 mg PIP q.d. and from 62.8% to 85.2% for the 120 mg PIP single dose

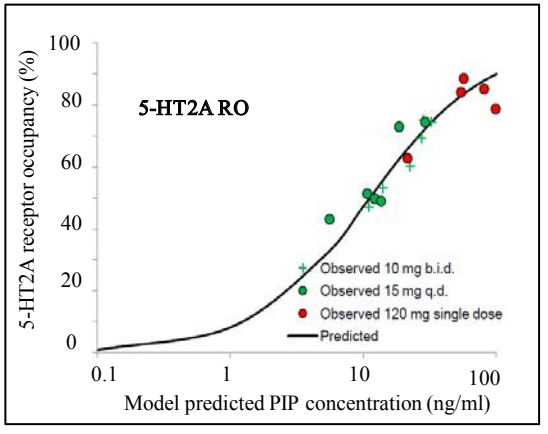
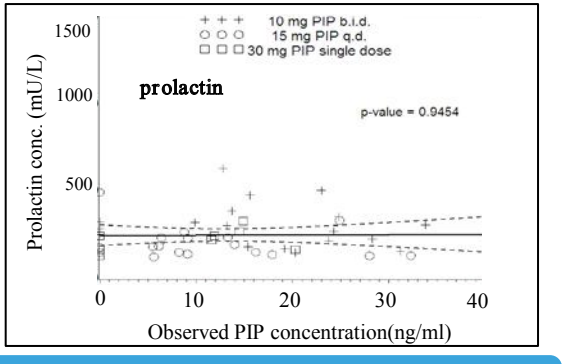


Figure 3:PIP treatment up to 30 mg/d did not increase prolactin levels.
Scatter plot of the PIP conc. versus serum prolactin conc. for the low dose PIP treatments (lin.regr & 95% CI)



Discussion and Conclusion

After 15 mg q.d. dosing mean steady-state plasma concentrations of PIP fluctuated between 9.8 and 21 ng/mL and after a single high dose of 120 mg PIP mean C_{max} was 152 ng/mL (Table 1). A two-compartmental model adequately described the PK of PIP and there was no indication for hysteresis (Figure 1). A sigmoidal model was used to characterize the relationship between 5-HT2A RO and plasma concentration of PIP (Figure 2). 5-HT2A RO ranged from 43.2% to 75.2% for the 10 mg PIP b.i.d. and 15 mg PIP q.d. and from 62.8% to 85.2% for the 120 mg PIP single dose with EC_{50} estimated at 11.2 ng/mL (95% CI from 9.62 to 12.8 ng/mL). D2 RO ranged from 4% to 33% for PIP concentrations not exceeding 24.5 ng/mL. No increase in prolactin concentration was observed for PIP concentrations up to 35 ng/mL (Figure 3).

In conclusion, plasma concentrations of low-dose pipamper one (5mg b.i.d.) that were effective in enhancing the antidepressant effect of citalopram in a proof-of-concept study correspond to about 50-60% receptor occupancy of 5-HT2A on average, and very low receptor occupancy of D2. This target binding range can be obtained not only with a twice daily but also with a once daily dosing regimen of low-dose pipamperone.

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