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Selective Serotonergic Properties of Low-Dose Pipamperone May Enhance Antidepressant Effect: Preclinical Evidence

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Introduction

- It is widely accepted that selective serotonin reuptake inhibitors (SSRIs) are a first-line therapy for major depressive disorder (MDD).[1]
- SSRIs generally have a slow onset of therapeutic effect and low rate of response and remission.[2]
- When response to SSRI monotherapy is unsatisfactory, one approach is to augment therapy with a second medication.[3]
- Drugs antagonizing 5-HT_{2A} receptors can provide effective augmentation of SSRI monotherapy[4]; the mechanism may involve inhibition of negative feedback on serotonergic neurons that occurs in response to elevated levels of synaptic 5-HT caused by SSRIs.[5,6]
- Combining a SSRI with a drug that leads to additional and selective inhibition of D_4 and 5-HT_{2A} receptors may generate additive and potentially synergistic antidepressant effects by restoring the balance between dopamine (DA) and 5-HT in the limbic system and cortical areas and by increasing both DA and 5-HT tonus while blocking undesired 5-HT_2 receptor activation.
- The neuroleptic pipamperone is a high-affinity antagonist of 5-HT_{2A} and D_4 receptors and a low-affinity antagonist of D_2 receptors.[7,8]

Objective

- To identify a dose of pipamperone that is high enough to have substantial 5-HT_{2A} antagonism but low enough to have no relevant D_2 antagonism

Methods

Study Design

- To identify appropriate pipamperone doses, a modified version of the apomorphine-tryptamine-norepinephrine (ATN)–test[9] was done in rats.
- Pharmacokinetic and pharmacodynamic modeling was used to predict the binding of pipamperone at relevant plasma concentrations to 5-HT_{2A}, D_4, D_2, α_1, 5-HT_{2C}, and H_1 receptors in patients.
- Protocols were reviewed and approved by the Institutional Animal Review Board and complied with the Declaration of Helsinki.

ATN-Test

- Male Wiga Wistar rats (Charles River, Germany; n=5 per dose) were injected with pipamperone (0.04, 0.08, 0.16, 0.31, 0.63, 1.25, 2.5, 5.0, or 10 mg/kg subcutaneous) or control (test solvent) and challenged with apomorphine (1.0 mg/kg intravenous [IV]) at 30 minutes, tryptamine (25 mg/kg IV) at 90 minutes, and norepinephrine (1.25 mg/mL IV) at 120 minutes.
- Behavioral and physiologic effects on dopamine, 5-HT, and norepinephrine neurotransmitter systems were scored.
  - After apomorphine challenge: stereotypy (0 = absent, 1 = slight, 2 = moderate, 3 = pronounced) and palpebral opening (1 = one quarter open, 2 = half open, 3 = three quarters open, 4 = wide open, 5 = exophthalmos)
  - After tryptamine challenge: bilateral clonic seizures of the forepaws (0 = absent, 1 = slight, 2 = moderate, 3 = pronounced), palpebral opening (1–5), and hyperemia and cyanosis of the ears (0 = absent, 1 = slight, 2 = moderate, 3 = pronounced)
  - After norepinephrine challenge: α_1 receptor–mediated mortality at 15 minutes (yes/no)

Pharmacokinetic/Pharmacodynamic Modeling

- In vivo K_d values for pipamperone binding to the 5-HT_{2A}, D_4, D_2, α_1, 5-HT_{2C}, and H_1 receptors after twice-daily (BID) dosing were predicted from in vitro pK_i values obtained from literature and corrected based on results of a plasma protein–binding study.
- Assuming sigmoidal binding (using predicted in vivo K_d and Hill coefficient of 1), occupancy of the 5-HT_{2A}, D_4, D_2, α_1, 5-HT_{2c}, and H_1 receptors after BID dosing was predicted for steady-state plasma concentrations of pipamperone that were determined based on literature values in healthy volunteers and assuming linear pharmacokinetics.

Statistical Analysis

- Median effective dose (ED_{50}) and corresponding 95% confidence limits (CLs) were determined using the Spearman-Kaerber estimate[10] with theoretical instead of empirical probabilities to allow tabulation as a function of the slope of the log dose-response curve.

Results

ATN-Test

- ED_{50} values for pipamperone in the ATN-test are shown in **Table 1**.

Table 1. Median Effective Doses of Pipamperone for Selected Effects in the ATN-Test

Challenge	ED_{50} (95% CL), mg/kg
Apomorphine, 1.0 mg/kg IV	
Inhibition of stereotypy	1.55 (0.96, 2.50)
Decrease of palpebral opening	4.40 (3.30, 8.70)
Tryptamine, 25 mg/kg IV	
Reversal of cyanosis	0.34 (0.22, 0.51)
Inhibition of bilateral convulsions	0.13 (0.08, 0.21)
Decrease of palpebral opening	1.78 (1.10, 2.87)
Norepinephrine, 1.25 mg/kg IV	
Protection against lethality	>10.0

ATN=apomorphine, tryptamine, norepinephrine; CL=confidence limit; ED_{50}=median effective dose.

- At very low doses, pipamperone inhibited tryptamine-induced cyanosis (ED_{50}, 0.34 mg/kg) and bilateral convulsions (ED_{50}, 0.13 mg/kg), indicating blockade of peripheral and central 5-HT_{2A} receptors, respectively.
- At higher doses (ED_{50}, 1.55–4.40 mg/kg), pipamperone inhibited apomorphine-induced stereotypy (a D_2 receptor–mediated effect) and decreased palpebral opening after the tryptamine and apomorphine challenges (possible α_1 receptor–mediated effects).
- Pipamperone doses of up to 10 mg/kg did not affect norepinephrine-induced lethality.

Pharmacokinetic/Pharmacodynamic Modeling

- **Table 2** shows the in vitro pK_i values for the 5-HT_{2A}, D_4, D_2, α_1, 5-HT_{2C}, and H_1 receptors and the expected corresponding plasma concentrations of pipamperone required to achieve these values in vivo.
  - These concentrations are above the K_i value for the 5-HT_{2A} and D_4 receptors **(Table 2)**.

Table 2. Expected Plasma Concentrations of Pipamperone Required to Achieve In Vitro pK_i Values for 5-HT_{2A}, D_4, D_2, α_1, 5-HT_{2C}, and H_1 Receptors In Vivo

Receptor	pK_i, M	Pipamperone Total Plasma Concentration, ng/mL
5-HT_{2A}	8.2	4
D_4	8.0	6
D_2	6.7	117
α_1	7.2	37
5-HT_{2C}	6.9	71
H_1	5.7	1171

- Predicted receptor occupancy at C_{avg} with 2.5–120 mg/kg pipamperone BID is shown in **Table 3**; pipamperone 5.0 mg BID was predicted to produce a C_{avg} that would achieve high occupancy of 5-HT_{2A} and D_4 receptors and limited occupancy of D_2, α_1, 5-HT_{2C}, and H_1 receptors.
  - Simulations predicted 5.0 mg pipamperone BID would produce a steady-state maximum concentration of approximately 18 ng/mL and a steady-state average concentration (C_{avg}) of approximately 11 ng/mL **(Table 3)**.

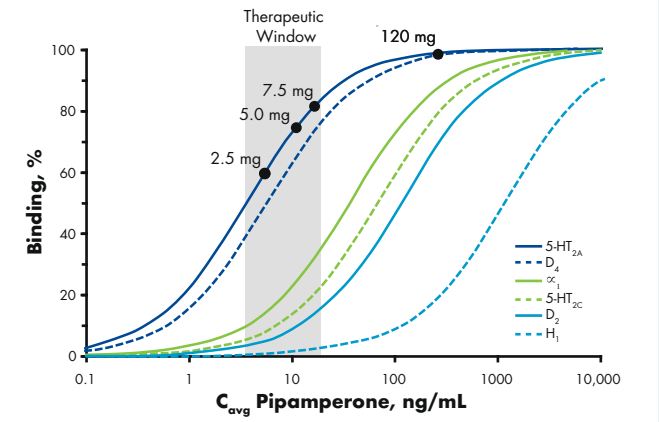
Table 3. Predicted Binding to 5-HT_{2A}, D_4, D_2, α_1, 5-HT_{2C}, and H_1 Receptors at Average Plasma Concentrations Achieved With 2.5–120 mg/kg Pipamperone BID

		Binding, %					
Pipamperone BID Dose, mg	C_{avg}, ng/mL	5-HT_{2A}	D_4	D_2	α_1	5-HT_{2C}	H_1
120	263	99	98	69	88	79	18.3
7.5	16	82	74	12	31	19	1.4
5.0	11	75	65	9	23	13	0.9
2.5	5	60	48	4	13	7	0.5

BID=twice daily; C_{avg}=average concentration at steady state.

- **Figure 1** shows predicted efficacy of pipamperone at C_{avg} in patients in vivo.
  - Efficacy was predicted with ≥60% occupancy of the 5-HT_{2A} receptor and ≥40% occupancy of the D_4 receptor, corresponding to doses ≥2.5 mg BID.
- **Figure 1** shows predicted tolerability of pipamperone at C_{avg} in patients in vivo.
  - Adverse events were predicted to occur with >10% occupancy of D_2 and H_1 receptors, corresponding to doses ≥7.5 mg BID.
- The optimal dose range of pipamperone for augmenting antidepressant efficacy in patients without neuroleptic effects was predicted to be 2.5–7.5 mg BID.

Figure 1. Predicted Clinical Efficacy and Tolerability of Pipamperone



C_{avg}=average concentration at steady state.

Conclusions

- **At very low doses (ED_{50}, 0.13–0.34 mg/kg), pipamperone inhibited tryptamine-induced cyanosis and bilateral convulsions in rats, indicative of blockade of peripheral and central 5-HT_{2A} receptors, respectively.**
- **Inhibition of apomorphine-induced stereotypy, a D_2 receptor–mediated effect, occurred only at higher doses (ED_{50}, 1.55 mg/kg).**
- **Addition of low-dose pipamperone to SSRI monotherapy may improve antidepressant efficacy and accelerate symptom resolution in patients with MDD via selective 5-HT_2/D_4 receptor antagonism.**
- **Pharmacokinetic/pharmacodynamic modeling predicted an optimal pipamperone dose between 2.5 and 7.5 mg BID in patients for effectively blocking 5-HT_2 and D_4 receptors without significantly affecting D_2 receptors. This dose is well below clinical doses presently used in EU countries[11]; pipamperone is not approved in the United States.**

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