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Clinical and pharmacological review on novel melatonergic antidepressant: Agomelatine

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ABSTRACT

Agomelatine is a new agent with a unique pharmacological outline, as it is the first melatonergic antidepressant. It has potential role in the treatment of patients with major depressive disorder (MDD). Agomelatine (trade names Valdoxan, Melitor, Thymanax) is a chemical compound that is structurally closely related to melatonin. Agomelatine has a new pharmacological mechanism of action, which combines melatonin MT1 and MT2 agonist properties with a serotonin 5-HT_{2C} antagonist effect. Agomelatine was rapidly and well ($\geq 80\%$) absorbed after oral administration. Because of its action upon the melatonin receptors, agomelatine shows a marked improvement in sleep quality.

Key words: Agomelatine, Major Depressive Disorder (MDD)

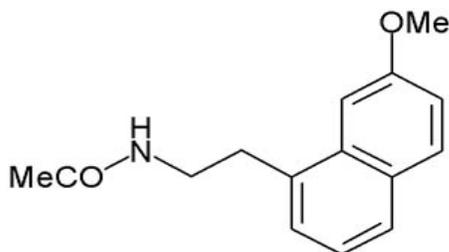
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INTRODUCTION

Agomelatine (N-[2-(7-methoxynaphthalen-1-yl) ethyl] acetamide), its antidepressant efficacy has been verified in the treatment of major depressive disorder (MDD) at a dose of 25 mg/day. It has a new pharmacological mechanism of action, which combines melatonin MT1 and MT2 agonist properties with a serotonin 5-HT_{2C} antagonist effect. The 5-HT_{2C} receptors are considered a relevant target with regard to antidepressant therapy, as several currently used antidepressant drugs are endowed with 5-HT_{2C} receptor antagonist properties (e.g. mianserin and mirtazapine). Agomelatine showed significant benefits over paroxetine due to the complete absence of side effects including the associated sexual side effects that are troublesome with some antidepressants. Because of its action upon the melatonin receptors, agomelatine shows a marked improvement in sleep quality. Agomelatine has also proven to have anxiolytic properties and thus may prove to be very useful in the treatment of anxiety disorders [1].

Chemical structure

Systematic (IUPAC) name [2]: N-[2-(7-methoxynaphthalen-1-yl) ethyl]acetamide



Molecular Formula: C₁₅H₁₇NO₂

Molecular Mass: 243.301

Physical properties [3]

Appearance: White or white like crystal powder or supplied as a crystalline solid.

Solubility: Agomelatine is a non-hygroscopic white or almost white powder practically insoluble in purified water and contains no asymmetric carbon atoms. Agomelatine is soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide. The solubility of agomelatine in these solvents is approximately 30 mg/ml. Agomelatine is sparingly soluble in aqueous buffers. For maximum solubility in aqueous buffers, agomelatine should first be dissolved in ethanol and then diluted with aqueous buffer of choice. Agomelatine has a solubility of approximately 0.5 mg/ml in a 1:1 solution of ethanol: PBS (pH 7.2) using this method. Do not recommend storing the aqueous solution for more than one day.

Stability: Stability studies were carried out on three primary batches according to defined stability protocols, which follow the ICH guidelines on stability at 25°C/60% RH and at 30°C/70%RH during 18 months, at 30°C/60%RH during 12 months and 40°C/75%RH during 6 months. Physical and chemical parameters tested did not show significant signs of modifications in relation to the initial controls and comply with the shelf-life specifications.



Assay (HPLC): 99.0%min
Loss on drying: NMT0.5%
Identification: NMR, MS
Melting point: 108° C (Melting point of crystalline form VI of Agomelatine is 94° C.)
Single impurity :< 0.3%
Total impurities: <0.5%

Pharmaceutical Composition

Agomelatine	25g
Lactose monohydrate	62g
Magnesium stearate	1.3g
Povidone	9g
Silica, colloidal anhydrous	0.3g
Sodium cellulose glycolate	30g
Stearic acid	2.6g

*Formulation for the preparation of 1000 tablets each containing a dose of 25 mg.

Property	Specifications
Appearance	White to off-white crystalline powder or white alike crystal powder or supplied as a crystalline solid.
Solubility	Soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide. It is sparingly soluble in aqueous buffers.
Identification	NMR, MS
Absorption	230 nm
Melting point	108° C
Related substances	Single impurity: <0.3% Total impurity: <0.5%
Loss on drying:	NMT 0.5%
Assay(HPLC):	99.0% min

Dosage forms and strengths

Tablets-25mg

Dose: The proposed posology is 25 mg taken in the form of oral tablet in the evening. After two weeks of treatment, if further clinical improvement was required, the dose may be increased to 50 mg oral tablet once daily, taken as a single dose of two tablets in the evening.

Pharmacology [4]

Mechanism of action: Agomelatine is a potent agonist of melatonin (MT1 and MT2) receptors with 5-HT_{2C} antagonist properties. It is also a 5-HT_{2B} antagonist. Agomelatine does not interact with adenosine, adrenergic, dopamine, GABA, muscarinic, nicotinic, histamine, excitatory amino acid, benzodiazepine and sigma receptors, nor with sodium, potassium or calcium channels. Through its 5-HT_{2C} antagonist effect, agomelatine increases dopamine and noradrenaline release specifically in the prefrontal cortex.

Pharmacodynamics

Primary pharmacodynamics: Agomelatine is a melatonin agonist with high affinity binding to human melatonin MT1 and MT2 receptors. Agomelatine is also a serotonin antagonist at the 5-HT_{2C} receptor from man and several animal species, although with low affinity. Two of the three main metabolites of agomelatine showed some pharmacological activity at the melatonin receptors, while a third metabolite (dihydrodiolagomelatine, DHDP) was not pharmacologically active at either receptor families.

Secondary pharmacodynamics: Agomelatine showed chronobiotic activity related to the melatonin activity, and anxiolytic effects while no indication of antipsychotic properties was seen.

Pharmacokinetics [4]

Bioavailability: 78%

Half life : 2.3hours (may be)

Absorption-Bioavailability

Agomelatine was rapidly and well ($\geq 80\%$) absorbed after oral administration. Absolute bioavailability is low ($< 5\%$ at the therapeutic oral dose) and the interindividual variability is substantial.

In vitro the intestinal transport of agomelatine across a Caco-2 cell monolayer was high through passive diffusion and corresponded to a predicted in vivo human rapid and total absorption of the compound. In vivo, as reflected by the urinary recovery of radioactivity following oral administration of [3H]-agomelatine and [14C]-agomelatine gastrointestinal absorption was at least $81 \pm 4.2\%$ of the dose, and rapid ($T_{max} < 1h$).

The bioavailability is increased in women compared to men. The bioavailability is increased by intake of oral contraceptives and reduced by smoking.

Food intake (standard meal or high fat meal) did not modify the extent of bioavailability of agomelatine. Therefore agomelatine can be administered with or without meals. The variability is increased with high fat food. The peak plasma concentration is reached within 1 to 2 hours.

In the therapeutic dose-range, agomelatine systemic exposure increases proportionally with dose. At higher doses, a saturation of the first pass effect occurs.

Tissue Distribution and protein binding

Steady-state volume of distribution (V_{ss}) was determined as about 35L after i.v. administration of agomelatine and was dose independent. Agomelatine was bound to plasma proteins at 95% mainly to serum albumin (about 35%) and alpha1-acid glycoprotein (about 36%).

Metabolism and excretion

The main routes of metabolism in rat, monkey and man were as 3-hydroxylation, 7-desmethylation and oxidation of the naphthyl moiety at position 7, leading to the main metabolites 3HP, 7DP, and DHDP. The metabolites of agomelatine were conjugated and excreted via urine and faeces, and only low levels of unchanged agomelatine were excreted.

Clinical efficacy

The efficacy and safety of agomelatine in major depressive disorder were studied in a clinical development programme in which agomelatine was administered to more than 2400 patients and 400 healthy volunteers in 25 countries in Europe, Africa, South America, Australia and North America.

Adverse reactions

Adverse reactions were usually mild or moderate and occurred within the first two weeks of treatment. The most common adverse reactions were dizziness and nausea. These adverse reactions were usually transient and did not generally lead to cessation of therapy.

CONCLUSION

Agomelatine is a new agent with a unique pharmacological outline, as it is the first melatonergic antidepressant. Overall, agomelatine is a promising and well-tolerated medication for the treatment of major depressive disorder.

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