Available online at

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Int J Pharm Biomed Res 2010, *1*(3), 113-116

International Journal of PHARMACEUTICAL AND BIOMEDICAL RESEARCH

ISSN No: 0976-0350

Review article

A novel atypical antidepressant drug: Agomelatine - A review

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Received: 23 Sep 2010 / Revised: 26 Sep 2010 / Accepted: 26 Sep 2010 / Online publication: 27 Sep 2010

ABSTRACT

Agomelatine, a synthetic analog of hormone melatonin belongs to a new class of atypical antidepressant with a novel mechanism of action at melatoninergic and serotoninergic receptors which distinguishes it from the other currently available antidepressants. It acts on MT1 and MT2 receptors normalizing the disturbed circadian rhythms and disrupted sleep-wake cycles, apart from inhibiting 5HT-2C receptor involved in the mood, motor and cognitive deficits associated with depressive states. It is an effective alternative for patients who do not respond to or cannot tolerate currently available antidepressant agents. Subsequent comprehensive pharmacological evaluation and extensive clinical trials, agomelatine was granted marketing authorization in 2009 for the treatment of major depression in Europe, thereby becoming the first approved antidepressant to incorporate a non-monoaminergic mechanism of action. This article reviews the significance and pharmacological aspects of a novel atypical antidepressant drug, agomelatine.

Key words: Agomelatine, Atypical antidepressant, Melatonin analogs

1. INTRODUCTION

Mood disorders constitute a major public health problem and have been projected by WHO to rank second to all diseases by 2010 [1]. The prevalence of psychiatric disorders differ between countries and within countries across various ethnicities. Depression is a major disorder of mood affecting 340 million people world over [2]. Chronic and recurrent depression can disrupt the normal physical, mental, social life of patients and their families and it can also drive an individual to commit suicide. Thus it has an effect on the health care system making it essential to be diagnosed at the earliest and treated. The goal of treatment of major depressive disorder (MDD) is remission of all symptoms with complete recovery of social and vocational dysfunction.

Currently available antidepressants increase monoamine levels in locus coeruleus, raphe nucleus and mediate neurogenesis in hippocampus. Use of tricyclic antidepressants (TCA) is limited to nonresponders to selective serotonin reuptake inhibitors (SSRIs) and selective serotonin norepinepherine reuptake inhibitors (SNRIs) because TCA's have poor tolerability profile and lethality in higher dose. SSRIs are effective in mild to moderate depression and they are widely used because they are safe in overdose and cost effective but are associated with side effects like discontinuation symptoms, sexual dysfunction, gastrointestinal (GI) disturbances and weight gain [3].

Only 30-40% of patients achieve remission with the above treatment modalities [3]. A significant proportion of patients has inadequate response or stops the medications due to intolerable side effects. Failure to achieve remission increases the risk of relapse or recurrence with worsening of long term prognosis. Thus clearly, there is an unmet need for an antidepressant which is relatively more efficacious and better tolerated than SSRIs and TCA.

This review focuses on the role of agomelatine, an antidepressant with a novel mechanism of action at melatoninergic and serotoninergic receptors which distinguishes it from the other currently available antidepressants. Agomelatine has been investigated extensively in preclinical studies. It is approved by the European Medicines Agency for the treatment of depression and is marketed throughout the European Union from 19th February 2009 [4]. A clinical trial for agomelatine is being conducted in United States of America and is yet to be approved by the US FDA [5].

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2. PATHOGENESIS OF DEPRESSION

The cause and pathophysiology of depression is unclear. Many hypotheses have been put forth to explain the occurrence of depression in susceptible individuals. The monoamine hypothesis explains that depletion of monoamines like serotonin (5 HT), norepinephrine (NE) in the hippocampus, limbic system and frontal cortex are responsible for the depressive symptoms [3]. There is interindividual variation in symptoms and the existing antidepressants which act by increasing these monoamine levels have been completely effective in less than 50% of patients [6]. Thus monoamine hypothesis fails to fully explain the pathophysiology of depression resulting in search for newer drug therapies with a novel mechanism of action.

New evidence has shown that disruption of circadian rhythm can predispose to depression. Melatonin, the hormone from the pineal gland regulates various circadian rhythms like body temperature; cortisol secretion, sleep–wake cycles, rapid eye movement (REM) sleep and slow-wave sleep [6]. In patients with depression, the melatonin levels are low which delays the circadian rhythm mentioned above and this has been proposed to be a "trait marker" for depression [7]. Patients with depression may manifest with delayed onset of sleep, difficulty in maintaining sleep and early morning awakening. Evidence has shown that resetting of disrupted circadian rhythm may play a pivotal role in the treatment of this condition [6].

In mammals, circadian rhythm originates in the suprachiasmatic nucleus (SCN) in the hypothalamus which has abundant melatoninergic receptors. There are two distinct forms of melatoninergic receptors, the MT1 and MT2, which are responsible for sleep promoting and circadian effects of melatonin. The MT1 receptors mediate the acute inhibition of neuronal firing within the SCN and the MT2 receptors are responsible for inducing phase shifting (like delay in cortical secretion or onset of sleep) of circadian rhythm [6].

3. CHEMISTRY OF AGOMELATINE

Agomelatine is a synthetic analog of hormone melatonin [8]. Agomelatine is N-[2-(7-methoxynaphthalen-1-yl) ethyl] acetamide.

4. MECHANISM OF ACTION

This compound binds to the melatoninergic receptors and the serotoninergic 5-HT2c receptor giving rise to the Melatonin Agonist and Selective Serotonin Antagonist (MASSA) concept. The melatoninergic receptors MT1 and MT2, are G protein coupled receptors and they act through decreasing cAMP and cGMP. Agomelatine strongly binds to and stimulates the activity of MT1 and MT2 receptors normalizing the disturbed circadian rhythms and disrupted sleep-wake cycles [6]. Unlike the existing antidepressants, agomelatine does not inhibit the uptake of serotonin, norepinephrine or dopamine [9]. It inhibits 5HT-2C receptor (G protein coupled receptor which increases IP3/DAG secondary messenger system) found abundantly in the SCN, frontal cortex, hippocampus and basal ganglia involved in the mood, motor and cognitive deficits associated with depressive states [6]. 5HT-2C receptor antagonism increases norepinephrine and dopamine levels in the frontal cortex of the brain [10]. This action of agomelatine produces antidepressant, antianxiety and also increases slow-wave sleep which is decreased in depression [11]. It has been observed that it can increase neurogenesis in the hippocampus and may also have neuroprotective effects (by influencing glutamate release, glucocorticoid receptor gene expression and various neurotropic factors [12]) which might also contribute to its antidepressant effects [13]. A study has shown that agomelatine alleviates sleep disturbances after one week of therapy and by two weeks antidepressant effects manifest [14].

The combined actions of agomelatine at MT1, MT2, and 5HT-2C receptors can improve the disturbed circadian rhythm and abnormal sleep pattern thus produce the antidepressant effect. These unique effects suggest that it might be effective for the treatment of seasonal affective disorder like anxiety and bipolar depression.

5. PHARMACOKINETICS

Agomelatine on oral administration is rapidly absorbed with bioavailability of more than 78% [14]. Food slows the absorption of agomelatine, but it is clinically insignificant [12]. It peaks in plasma after 1 to 2 h following oral administration. It is more than 95% plasma protein bound with 35% bound to albumin and 36% bound to α-1 acid glycoprotein.[14] In vitro studies have established that agomelatine is unlikely to cause displacement of highly protein bound drugs but in vivo studies are lacking in this regard [12]. The volume of distribution is around 35 L [14]. 90 % of the administrated dose is metabolised by cytochrome P450 1A2 isoenzyme to 7-O –demethylated and hydroxylated inactive metabolites [12]. About 61 to 81 % of the dose is excreted as metabolites in urine over the first 24 h with the mean terminal half life of 2 to 3 h [14]. It is also metabolised to 3,4 dihydrodiol which is excreted in faeces. Moderate hepatic impairment increases (100 times) drastically the plasma levels of agomelatine but a small increase (>25%) in renal impairment [12].

6. DOSE AND PRECAUTIONS

The effective dose of agomelatine is 25 mg per day given once at bed time for two weeks and can be increased to 50 mg per day in patients with inadequate response. Night time dosing is recommended because agomelatine improves the quality of sleep without day time sedation [9]. Sublingual agomelatine at the dose of 0.5-2mg once daily is under clinical trial for the management of depression [5]. The

specific data on safety for its use in pregnancy and lactating mothers is not available [4] but animal studies have not shown any risk [9]. Agomelatine is not recommended for use below 18 years of age and should be used with caution in the elderly (≥ 66 years of age) due to lack of clinical data [12].

7. DRUG INTERACTIONS

It does not induce or inhibit the Cytochrome p450 enzymes but enzyme inducers like omeprazole and nicotine decrease the serum levels of agomelatine hence the dose has to be increased to 50 mg per day when these drugs are concomitantly taken [9,12]. Fluoxamine and oestrogens have been found to increase the levels of agomelatine because of their enzyme inhibition. Other enzyme inhibitors like paroxetine, fluconazole, lithium, lorazepam, alcohol and valproic acid have insignificant interaction with Agomelatine [12].

8. USES

- Major depressive disorder especially in non-responders and intolerant to SSRIs
- Generalized anxiety disorder [15]
- Bipolar depression
- Sleep disturbances [16]
- Migraine and cluster headaches [17]

9. ADVERSE EFFECTS

Various clinical studies have shown that agomelatine is well tolerated and the adverse effect profile is similar to placebo [12]. Most common adverse effects are headache, nausea, dizziness, dry mouth, diarrhoea, insomnia, somnolence, constipation, fatigue, upper abdominal pain [12,16]. The most serious adverse effect was dizziness for which patients discontinued therapy with agomelatine [16].

10. ADVANTAGES OF AGOMELATINE

Agomelatine has a good tolerability profile compared with other antidepressants.

- Abrupt withdrawal of agomelatine (after 12 weeks of therapy) is not associated with discontinuation symptoms which are seen with existing antidepressants. Hence dose tapering is not needed in patients on agomelatine therapy [16].
- Serotonin syndrome, suicidal tendencies, cardiovascular effects (arrhythmias and hypotension) and weight gain have not been observed [16].
- Studies have shown to cause minimal GI disturbance and sexual dysfunction [12].
- Efficacy is similar to SSRIs and relapse rate is less compared to all the other antidepressants [4,12].
- Improves the quality of sleep (onset of sleep, increase slow wave sleep- deepest stage of sleep) without day time sedation [9]. Agomelatine administration at bed time coincides with endogenous secretion of melatonin (2 h prior to habitual bed time) [18].

11. CLINICAL TRIALS

Dose finding and efficacy study: 25 mg of agomelatine once daily at bed time was significantly effective when compared to placebo. In the same study 50 mg dose was used when patient showed inadequate response to 25 mg to which the patients responded. The adverse events in these studies were comparable to placebo. [19,20,21].

Early onset of efficacy: Agomelatine has quick onset of action detectable from 7th day after starting treatment as compared to venlafaxine [22].

With active comparators: Agomelatine demonstrated greater efficacy than venlafaxine and sertraline at 6 months [23,24].

Sleep and day time functioning: Agomelatine was superior to venlafaxine and sertraline in "getting to sleep and quality of sleep". There was also a significant difference in agomelatine group in "ease of awakening" at 2 weeks and 18 weeks compared to venlafaxine but not with sertraline [23,24].

Relapse and remission: Goodwin *et al* have shown significantly lower relapse and remission rate compared to placebo when patients were followed till 24 weeks [25]. An insignificant difference in remitar status at 6 weeks between agomelatine and sertraline or venlafaxine was observed [23, 24].

12. CONCLUSIONS

Agomelatine is a novel atypical antidepressant with unique pharmacological profile that regulates the circadian rhythms with a relatively benign tolerability profile making it an effective alternative for patients who do not respond to or cannot tolerate currently available antidepressant agents. However the limitation with agomelatine is lack of long term active comparator controlled studies.

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