Agomelatine and its therapeutic potential in the depressed patient

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Abstract: Despite advances in understanding potential disease mechanisms and in developing novel therapeutic approaches to the treatment of major depressive disorder, the disease continues to carry an enormous personal, social, and economic burden. Agomelatine represents an important opportunity to advance the treatment of depression. It is a melatonergic (MT_1 and MT_2) agonist and serotonergic ($5HT_{2C}$) antagonist. Evidence from animal models of depression, complements emerging clinical data. In a dose range of 25–50 mg daily, agomelatine is an effective antidepressant with a very favorable side-effect profile. In particular, sleep restorative action in the absence of sedation and minimal effect on sexual function suggests that agomelatine represents a worthwhile treatment alternative for patients with major depressive disorder.

Keywords: agomelatine, major depressive disorder, antidepressant, efficacy, tolerability

Introduction

Major depressive disorder carries an enormous personal, social, and economic burden. Despite a better understanding of disease mechanisms and neurobiological consequences of treatments, the effectiveness and tolerability of currently available antidepressants remain suboptimal (Kennedy et al 2001; Trivedi et al 2006). The current search for therapeutic targets has shifted from selective monoamine systems to monoamine and non-monoamine networks (Millan 2004).

Although the selective serotonin reuptake inhibitor (SSRI) antidepressants induce substantial side-effects, including initial anxiety, nausea, insomnia, sexual dysfunction, and weight gain, their safety and tolerability profiles remain superior to those of tricyclic and monoamine oxidase inhibitor antidepressants. Unfortunately, the evidence to support superior efficacy of SSRIs is extremely limited. Dual action noradrenergic and serotonergic reuptake inhibitors (venlafaxine, duloxetine, milnacipran) appear to confer a modest advantage in remission rates compared with classical SSRIs (Lopez-Ibor et al 1996; Thase et al 2001; Smith et al 2002), but carry a similar side-effect burden to SSRIs (Vanderkooy et al 2002). Other mixed-action antidepressants, including trazodone, nefazodone, and mirtazapine, exert their antidepressant effects at least in part through antagonism of post-synaptic $5HT_{2A/2C}$ receptors. This action has a favorable effect on sexual function and sleep and has also been shown to enhance cortical release of dopamine and norepinephrine (Millan et al 2003).

Recent evidence from preclinical (Vacher et al 2002; Bourin et al 2004; Bertaina-Anglade et al 2006) and clinical (Loo et al 2002; Kennedy and Emsley 2006) studies suggests that agomelatine, a specific agonist of melatonergic-1 (MT_1) and melatonergic-2 (MT_2) receptors and an antagonist of $5HT_{2C}$ receptors (Audinot et al 2003; Millan et al 2003) has promising antidepressant properties (den Boer et al 2006). The role of MT_1 and MT_2 receptors in regulating the suprachiasmatic nucleus circadian clock suggests a mechanism to restore disruptions in the sleep-wake cycle and circadian rhythms.

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Chemistry and clinical pharmacology

Agomelatine is an acetamide naphthalene analog of melatonin that is dispensed in capsule form. Investigations of the action of agomelatine on over 80 receptors and enzymes revealed negligible affinity (IC50 > 10^{-5} M) for all potential targets except: MT_1 (KI = 0.1 nM); MT_2 (KI = 0.12 nM) (Audinot et al 2003); and $5HT_{2C}$ (pKi = 6.2 μM) (Millan et al 2003). Although it also interacted with $5HT_{2B}$ receptors, they are poorly represented in the central nervous system and have uncertain functional significance (Duxon et al 1997). Consequent studies investigating the effect of acute and chronic treatment with agomelatine on the density of $5HT_{1A}$ receptors and their coupling with G proteins in the dorsal raphe nucleus and the hippocampus in rats revealed no change in density (Hanoun et al 2004), in contrast to the action of a wide range of SSRI and tricyclic antidepressants (Pineyro and Blier 1999). In addition, agomelatine dose dependently blocked the induction of penile erections by $5HT_{2C}$ agonists and dose dependently enhanced dialysis levels of noradrenaline and dopamine in the frontal cortex, but not in the nucleus accumbens or striatum of freely moving rats (Millan et al 2003). No effect on serotonin levels was observed (Millan et al 2005).

Agomelatine is absorbed rapidly by the oral route and metabolized in the liver through cytochrome P450 1A2 and 2C9 isoenzymes, with metabolites predominantly excreted in urine (Bogaards et al 2000). The mean half-life of agomelatine is 2.3 hours. Co-administration of compounds that are metabolized by 1A2, including fluvoxamine, a potent inhibitor of the 1A2 isoenzyme system, may result in increased plasma levels of agomelatine, while inducers of 1A2 such as caffeine or nicotine are likely to reduce agomelatine levels.

Preclinical evidence

The focus of animal studies was to compare the effects of agomelatine with melatonin particularly in phase shifting and circadian rhythm effects. A program of research has also been developed to investigate potential antidepressant properties in a number of recognized animal models for anxiety and depression.

Melatonin plays a major role in the regulation of body temperature (Krauchi and Wirz-Justice 2001) and consolidation of sleep (Dijk and Cajochen 1997). Elevated levels of melatonin activate the MT_1 and MT_2 receptors. Activation of MT_1 receptors in the suprachiasmatic nucleus appears to inhibit neuronal firing and facilitate sleep, while activation of MT_2 receptors phase shift circadian rhythms (Dubocovich 2006). As a melatonin agonist, agomelatine

has also been shown to resynchronize circadian rhythms in animal models of delayed sleep-phase syndrome (Armstrong et al 1993; Redman et al 1995), in a dose-dependent and plasma-level-dependent manner (Martinet et al 1996). Unlike melatonin, however, agomelatine has anxiolytic properties in animal models of anxiety including the elevated plus maze, vogel conflict (Millan et al 2005; den Boer et al 2006) and social defeat (Tuma et al 2005) models. It has been postulated that these effects are related to the receptor profile (Millan et al 2005; Papp et al 2006).

Agomelatine has also demonstrated strong antidepressant-like properties in several animal models of depression, including chronic mild stress (Papp et al 2003), learned helplessness (Bertaina-Anglade et al 2002), forced swimming (Bourin et al 2004), and a psychosocial stress model in tree shrews (Fuchs et al 2006). These preclinical findings suggest that agomelatine, besides its antidepressant efficacy, may be helpful in sleep promotion and in resetting the biological clock in humans.

Two additional candidate mechanisms underlying depression involve abnormalities of glucocorticoid receptor function (van Rossum et al 2006) and hippocampal neurogenesis (Duman and Monteggia 2006). Using transgenic mice with impaired glucocorticoid receptor function, Barden et al (2005) concluded that the behavioral effects of agomelatine are not associated with changes in hypothalamic-pituitary-adrenal axis activity. However, in another animal model of depression (the tree-shrew), Simon and colleagues (2004) showed that agomelatine reversed the increases in cortisol, but this may be as an indirect consequence of its antidepressant activity.

In keeping with recent evidence that depression is associated with a reduction in granule cell neurogenesis in the hippocampus and that antidepressants from disparate classes promote neurogenesis (Malberg and Schechter 2005), Banasr and colleagues (2006) found that agomelatine increased both cell proliferation and survival of newly formed cells.

Clinical studies

Available data from published agomelatine trials address efficacy, dosing range, and tolerability with specific attention to sleep, sexual function, and abrupt discontinuation.

In an 8-week dose-finding study in over 700 patients, 3 doses of agomelatine (1 mg, 5 mg, and 25 mg/day) were compared with placebo, using paroxetine 20 mg as an active comparator. The analyses supported agomelatine 25 mg as the most effective dose, based on a significant difference from placebo on efficacy ($p < 0.05$) and rates of responders ($p < 0.05$) (Loo et al 2002). The

mean Hamilton Rating Scale for Depression (HAM-D; Hamilton 1960) score for the paroxetine group was also significantly lower than placebo (p < 0.05); however the rate of responders to paroxetine was not significantly different from placebo.

In a second study, Kennedy and Emsley (2006) evaluated agomelatine under placebo-controlled conditions for 6 weeks in 212 patients, with dose increase in a double blind fashion from 25 mg to 50 mg/day in patients who were considered to have not improved sufficiently after 2 weeks. Patients treated with agomelatine had a significantly lower mean HAM-D score at endpoint compared to placebo (14.1 ± 7.7 vs 16.5 ± 7.4, p = 0.026). A drug-placebo difference of 2–3 points is well within the range reported for currently available antidepressants. Using a response criterion of 50% reduction or more from baseline on HAM-D, there was a significantly higher rate of response with agomelatine compared with placebo (49.1% vs 34.3%, p = 0.03).

In a sub-analysis involving the "severe subpopulation" (defined as those with a baseline HAM-D of 25 or higher), treatment with agomelatine resulted in a significantly lower mean HAM-D total score at endpoint compared with placebo (14.4 ± 7.9 vs 17.3 ± 7.2, p = 0.024) and a significant difference in the percentage of responders compared with placebo (48.7% vs 30.7%, p = 0.024). This study also evaluated the effect of a dose increase from 25 mg to 50 mg in approximately one third of agomelatine- and placebo-treated patients, demonstrating a significant advantage of the 50 mg dose over placebo (p = 0.045).

Agomelatine has also been compared with venlafaxine in two separate randomized double-blind trials (Kennedy and Guilleminault 2006). In a 12 week trial, 277 subjects were randomized to receive agomelatine at a fixed dose of 50 mg or venlafaxine XR 75 mg, increased to 150 mg after 2 weeks. Although the primary outcome measure was change in sexual function among sexually active remitted subjects, a secondary analysis showed that remission (defined as a final score of 12 or less on the Montgomery Asberg Depression Rating Scale [MADRS; Montgomery and Asberg 1979]) was achieved by a comparable percentage of agomelatine- and venlafaxine XR-treatment patients. A second study was primarily designed to compare subjective reports of sleep patterns. In a flexible dosing, 6 week design, 165 patients were randomized to receive agomelatine (25–50 mg) and 167 were randomized to venlafaxine in the immediate release form (75–150 mg). Both groups experienced similar reductions in HAM-D scores and comparable percentage

of responders (based on the usual 50% reduction from baseline) (Kennedy and Guilleminault 2006).

Preclinical evidence that agomelatine has anxiolytic effects is enhanced by findings that anxiety symptoms in depressed patients are also responsive to agomelatine. In the original dose-finding study, anxiety symptoms were assessed using the Hamilton Anxiety Rating Scale (HAM-A; Hamilton 1959). In this study, agomelatine 25 mg daily, but not agomelatine 1 mg or 5 mg, significantly decreased anxiety symptoms compared with placebo (p < 0.05) (Loo et al 2002): further investigation is warranted in patients with anxiety disorders.

There is also preliminary evidence from an open-trial that agomelatine added to lithium or valproate rapidly reversed bipolar depression, supporting further investigation of agomelatine in bipolar disorder (Guelfi and Calabrese 2005). Results from a relapse prevention study are required to confirm the benefits of agomelatine as a maintenance treatment in depression.

Special issues with agomelatine
Restoration of the sleep-wake cycle
Sleep disturbance is an omnipresent depressive symptom, which is helped by most currently available antidepressants. Unfortunately, effective hypnotic doses may also be accompanied by daytime drowsiness (eg, mirtazapine; Radhakishun et al 2000) or by disrupted sleep architecture (eg, fluoxetine; Wilson and Argyropoulos 2005). Preclinical findings that agomelatine restores circadian rhythms (Armstrong et al 1993; Redman et al 1995) are further endorsed by evidence that agomelatine can phase shift temperature and hormonal release in healthy older men (Leproult et al 2005). With evidence to suggest that disruptions of the internal circadian rhythm system and the sleep-wake cycle may be relevant in the pathoetiology of depression (Boivin 2000), agomelatine should be particularly beneficial in restoring a healthy sleep-wake cycle.

In a polysomnographic study in 15 depressed patients, agomelatine over 6 weeks produced clinically significant improvements in reducing wake time after sleep onset, increasing total slow-wave sleep, and was also associated with favorable self reports of better quality of sleep and lack of daytime sleepiness (Quera-Salva et al 2005). The Cyclic Alternating Pattern (CAP) in non-rapid-eye-movement sleep was also significantly improved after 7 days treatment with agomelatine compared with placebo (Lopes et al 2005). There were also significant subjective advantages reported on the Leeds Sleep Evaluation Questionnaire (LSEQ; Parrott and

Hindmarsh 1978) on subjective sleep perceptions of "getting to sleep" and "quality of sleep" with agomelatine compared with venlafaxine after 1 week that remained significant for the remainder of the 6 week trial (Guilleminault 2005). Together, these preliminary reports on sleep emphasize the early and sustained restorative effects of agomelatine in the absence of other adverse effects on sleep.

Sexual function

Sexual function (particularly drive and desire) is frequently impaired in untreated depression (Kennedy et al 1999) and treatment-emergent sexual dysfunction (more often in arousal, orgasm, or ejaculation difficulties) occurs with most currently prescribed antidepressants (Kennedy et al 2000; Clayton et al 2002) Mirtazapine represents an exception to this pattern of antidepressant-induced sexual dysfunction, a result that is thought to be related to its $5HT_{2C}$ antagonist properties (Montgomery et al 2002). Since agomelatine also blocks the $5HT_{2C}$ receptor, it has been of considerable interest throughout the drug development program to systematically evaluate sexual function before and during agomelatine treatment in depressed patients. The sexual profile of agomelatine has consistently emerged as favorable, whether in studies using specific rating scales (Sex Effects Scale [SexFX; Kennedy et al 2006] or Arizona Sexual Experience Scale [ASEX; McGahuey et al 2000]) or based on spontaneously reported adverse events (Kennedy 2006). In one of these reports, sexual side-effects were compared in a depressed population during treatment with agomelatine and venlafaxine over 12 weeks. A significantly greater percentage of sexually active remitted patients in the agomelatine group reported no sexual dysfunction (80%) compared with just over 50% in the venlafaxine group (Kennedy 2005). Spontaneously reported sexual side-effects with agomelatine were also not different from placebo (Kennedy 2006).

General aspects of safety and tolerability

Agomelatine has a favorable side-effect profile that has been indistinguishable from placebo in several clinical trials (Loo et al 2002; Kennedy and Emsley 2006) and superior to paroxetine – paroxetine showed significantly more gastrointestinal side-effects than placebo (Loo et al 2002). There have been no more reports of adverse effects on cardiovascular, hepatic, or renal function and no other laboratory abnormalities with agomelatine than with placebo.

The effect of abruptly discontinuing agomelatine has been evaluated in a double-blind, placebo-controlled comparison with paroxetine (Montgomery et al 2004). After 12 weeks of double-blind treatment with agomelatine 25 mg or paroxetine 20 mg daily, sustained remitted depressed patients were randomized for 2 weeks to remain on their index antidepressant or switch to placebo. Discontinuation emergent signs and symptoms were evaluated using a validated scale (Rosenbaum et al 1998). In contrast to the paroxetine discontinuation group, there was no increase in discontinuation emergent signs and symptoms in the group who abruptly discontinued agomelatine.

Conclusion

As an antidepressant with unique effects on melatonergic and $5HT_{2C}$ receptors, agomelatine represents a promising advance in the treatment of major depressive disorder. Beyond a role in treating major depressive disorder, agomelatine may also represent a treatment option for other disorders including bipolar disorder, and generalized anxiety disorder.

Disclosures

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