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Treatment of premenstrual dysphoric disorder with the $GABA_A$ receptor modulating steroid antagonist Sepranolone (UC1010)—A randomized controlled trial

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ABSTRACT

Context: Allopregnanolone is a metabolite from progesterone and a positive modulator of the $GABA_A$ receptor. This endogenous steroid may induce negative mood in sensitive women when present in serum levels comparable to the premenstrual phase. Its endogenous isomer, isoallopregnanolone, has been shown to antagonize allopregnanolone effects in experimental animal and human models.
Objective: The objective was to test whether inhibition of allopregnanolone by treatment with the $GABA_A$ modulating steroid antagonist (GAMSA) Sepranolone (UC1010) during the premenstrual phase could reduce symptoms of the premenstrual dysphoric disorder (PMDD). The pharmacokinetic parameters of UC1010 when given as a subcutaneous injection were measured in healthy women prior to the study in women with PMDD.
Design: This was an explorative randomized, double-blind, placebo-controlled study.
Setting: Swedish multicentre study with 10 centers.
Participants: Participants were 26 healthy women in a pharmacokinetic phase I study part, and 126 women with PMDD in a phase II study part. Diagnosis followed the criteria for PMDD in DSM-5 using Daily Record of Severity of Problems (DRSP) and Endicott's algorithm.
Intervention: Subjects were randomized to treatment with UC1010 (10 or 16 mg) subcutaneously every second day during the luteal phase or placebo during one menstrual cycle.
Outcome measures: The primary outcome measure was the sum of all 21 items in DRSP (Total DRSP score). Secondary outcomes were Negative mood score i.e. the ratings of the 4 key symptoms in PMDD (anger/irritability, depression, anxiety and lability) and impairment (impact on daily life).
Results: 26 healthy women completed the pharmacokinetic phase I study and the dosing in the following trial was adjusted according to the results. 106 of the 126 women completed the phase II study. Within this group, a significant treatment effect with UC1010 compared to placebo was obtained for the Total DRSP score ($p = 0.041$) and borderline significance ($p = 0.051$) for the sum of Negative mood score.

Nineteen participants however showed symptoms during the follicular phase that might be signs of an underlying other conditions, and 27 participants had not received the medication as intended during the symptomatic phase. Hence, to secure that the significant result described above was not due to chance, a post hoc sub-group analysis was performed, including only women with pure PMDD who completed

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the trial as intended (n = 60). In this group UC1010 reduced Total DRSP scores by 75% compared with 47% following placebo; the effect size 0.7 (p = 0.006), and for sum of Negative mood score (p = 0.003) and impairment (p = 0.010) with the effect size 0.6. No severe adverse events were reported during the treatment and safety parameters (vital signs and blood chemistry) remained normal during the study.
Conclusions: This explorative study indicates promising results for UC1010 as a potential treatment for PMDD. The effect size was comparable to that of SSRIs and drospirenone containing oral contraceptives. UC1010 was well tolerated and deemed safe.

1. Introduction

Premenstrual dysphoric disorder (PMDD) affects 3–5% of women in fertile age (Sveindottir and Backstrom, 2000; Wittchen et al., 2002). The disorder is typified by a recurrent cluster of mental symptoms such as irritability, depressed mood, aggression and emotional lability that consistently recur only in the premenstrual (luteal) phase of the menstrual cycle (APA, 2013; O'Brien et al., 2011). Quality of life for these women is reduced due to a significant negative impact on social life, relations and work performance during the premenstrual period (Dennerstein et al., 2010). The pathophysiology of PMDD is not yet fully understood, but a temporal association with circulating ovarian steroids, in particular progesterone and its metabolite allopregnanolone (3α-OH-5α-pregnan-20-one), has been established (Backstrom et al., 2003). There are several lines of evidence suggesting the involvement of progesterone/allopregnanolone in PMDD. Most importantly, symptoms are relieved (or even abolished) when ovarian hormones are suppressed (Wyatt et al., 2004), and are reinstated when progesterone is administered (Segebladh et al., 2009). With the use of functional magnetic resonance imaging (fMRI), several studies report changes in brain reactivity across the menstrual cycle, most notably increased amygdala reactivity in the luteal phase (Toffoletto et al., 2014). Furthermore, throughout the brain, the highest concentration of progesterone is found in the amygdala (Bixo et al., 1997). The effect, however, is probably not induced by progesterone itself since the classical progesterone receptor antagonist, mifepristone (RU486), does not ameliorate the symptoms (Chan et al., 1994). Further, increasing evidence suggest that the symptoms are mediated by a progesterone metabolite, allopregnanolone, normally active as a positive modulator on the GABA(γ-amino-butyric acid)$_A$ receptor. Inhibition of progesterone conversion to allopregnanolone has been shown to ameliorate the symptoms in PMDD women (Martinez et al., 2016), and symptoms are strongly correlated to a specific level of allopregnanolone (Andreen et al., 2009).

Allopregnanolone is normally a potent positive GABA$_A$ receptor modulating steroid (Bristot et al., 2014) and like other positive GABA$_A$ receptor modulators, such as benzodiazepines and barbiturates, it has, in high concentrations, anaesthetic, antiepileptic and anxiolytic properties in animals and humans (Timby et al., 2006; van Broekhoven et al., 2007). Given its rapid conversion, serum levels of allopregnanolone mirror those of circulating progesterone across the menstrual cycle (Bixo et al., 1997; Wang et al., 1996). However, simple relationships (such as an excess or deficiency of allopregnanolone in women with PMDD) have not been established in systematic studies (Backstrom et al., 2003). Nevertheless, in women with PMDD the premenstrual mood improves when serum levels of allopregnanolone decrease (Martinez et al., 2016; Nyberg et al., 2007). Concentrations of allopregnanolone, corresponding to normal luteal phase levels, induce more severe mood changes than both higher and lower levels indicating a bimodal effect of allopregnanolone on mood (Andreen et al., 2006; Hommer et al., 1986). In line with these results, an abnormal response to physiological serum levels of ovarian steroids in women with PMDD was also shown by Schmidt et al. (Schmidt et al., 1998). In addition, fMRI studies have revealed a similar paradoxical response since a low oral dosage of progesterone, producing low serum concentration of allopregnanolone, increases amygdala reactivity, whereas a high dose decreases amygdala reactivity during an emotion discrimination paradigm (van Wingen et al., 2007; van Wingen et al., 2011). Similar bimodal/paradoxical effects are well described for other GABA$_A$ receptor agonists, e.g. benzodiazepines, in a subgroup of the general population (Bramness et al., 2006; Dougherty et al., 1996; Wenzel et al., 2002).

One likely reason for the altered response to allopregnanolone in PMDD is the plasticity of the GABA$_A$ receptor, since subunit composition and pharmacological properties has been shown to change with different reproductive states (Lovick et al., 2005; Maguire et al., 2005). For example, progesterone treatment or concentrations of progesterone/allopregnanolone across the estrous cycle, lead to an up-regulation of the α4,β,δ receptor subunits in the hippocampus, which, in turn, render the receptor more sensitive to the effects of allopregnanolone (Belelli et al., 2002; Shen et al., 2005). Studies in mice show that allopregnanolone can increase anxiety in situations of increased α4βδ GABA$_A$ receptor expression in hippocampus. In these studies, allopregnanolone is probably exerting its action on α4βδ containing GABA$_A$ receptors because this effect was not seen in δ- or α4-knock-out mice, and is probably acting as a negative modulator at α4βδ containing receptors under certain conditions (Shen et al., 2007; Shen et al., 2013).

In experimental studies of healthy women, intravenous allopregnanolone dose-dependently increase sedation and decrease maximal saccadic eye velocity (SEV). Measurement of SEV can be used to quantify GABA$_A$ receptor sensitivity (de Visser et al., 2003; Iacono and Lykken, 1981). In a recent study by us, women with PMDD were shown to have an altered sensitivity to an intravenous injection of allopregnanolone compared to healthy controls. PMDD women were more sensitive during the luteal phase of the menstrual cycle (Timby et al., 2016).

Allopregnanolone effects can be antagonized by its isomer isoallopregnanolone (Sepranolone; UC1010, 3β-OH-5α-pregnan-20-one) as shown in animal experiments (Backstrom et al., 2005; Lundgren et al., 2003; Shen et al., 2007; Stromberg et al., 2006), as well as in humans (Bengtsson et al., 2015). Isoallopregnanolone is a GABA$_A$ modulating steroid antagonist (GAMSA) and does not antagonize the effect of GABA itself or other GABA$_A$ agonists like benzodiazepines and barbiturates (Lundgren et al., 2003). When given intravenously to healthy women, isoallopregnanolone, does not cause any severe side-effects or adverse mood reactions as was shown in a pharmacokinetic study (Hedstrom et al., 2009). The hypothesis upon which the present study is based, is that the negative mood associated with PMDD is caused by the allopregnanolone-enhanced GABA-stimulated chloride uptake via primarily the GABA$_A$ receptor in the emotional center of CNS, and that women with PMDD have an altered sensitivity to the increase in allopregnanolone concentration during the luteal phase. The treatment rationale for UC1010 (isoallopregnanolone) is thus based