

Gyn-PhD1

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Allopregnanolone and mood: studies of postmenopausal women during treatment with progesterone

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Introduction

The addition of progestagens in sequential hormone therapy (HT) provokes negative mood symptoms in certain women. This action is supposed to be mediated through the gamma aminobutyric acid A (GABA_A) system, which is the major inhibitory system in the mammalian CNS. Allopregnanolone and pregnanolone, both neuroactive metabolites of progesterone, as well as benzodiazepines, barbiturates and alcohol act as positive modulators of the GABA_A receptor. Contradictory results from studies on the effect of GABA_A receptor modulators are reported. Beneficial properties such as anaesthesia, sedation, anticonvulsion and anxiolysis are reported in human and animal studies. However, recent reports have indicated occurrence of adverse, anxiogenic and aggressive effects. It has actually been suggested that several GABA_A receptor agonists, including allopregnanolone, have biphasic effects. Low concentrations increase an adverse, anxiogenic effect, whereas higher concentrations decrease this effect and show beneficial, calming properties.

Aims

To investigate if progesterone treatment induces adverse mood in postmenopausal women and if the severity in mood symptoms is related to progesterone, allopregnanolone or pregnanolone serum concentrations. Furthermore, the studies aimed at evaluating differences in serum progesterone, allopregnanolone and pregnanolone concentrations induced by different doses and routes of administration of progesterone.

Methods

Two randomised, placebo-controlled, double-blind crossover studies of postmenopausal women with climacteric symptoms were performed. In these studies postmenopausal women were used as a model to investigate adverse mood effects of progesterone treatment. Subjects were treated with estradiol continuously. Different doses of progesterone, given either vaginally or orally, were added sequentially during the last 14 days of each treatment cycle. Daily symptom ratings were kept using a validated rating scale. Blood samples for progesterone, allopregnanolone and pregnanolone analyses were collected during each treatment cycle. In addition, a study regarding the pharmacokinetics after ingestion of low-dose oral micronised progesterone (20 mg/40 mg) was conducted with postmenopausal women. Blood samples for the analyses of progesterone, allopregnanolone and pregnanolone were collected and pharmacokinetic parameters were calculated.

Results

Postmenopausal women on sequential HT with vaginal and oral micronised progesterone experience significant mood deterioration during the progesterone phase while on a low dose of progesterone but not on higher doses or the placebo. Negative mood symptoms occurred when

the serum concentration of allopregnanolone was similar to endogenous luteal phase levels, whereas lower and higher concentrations had no significant effect on mood. Mood deterioration during progesterone treatment resembles symptoms seen in women with premenstrual dysphoric disorder (PMDD) and, as earlier reported for PMDD, it was evident that only certain postmenopausal women experience adverse mood during progesterone treatment. In addition, pharmacokinetic analyses show that low-dose oral progesterone can be used as a prodrug to allopregnanolone when the aim is to achieve physiological concentrations of allopregnanolone in humans.

Conclusions

A bimodal association, which resembles an inverted U-shaped curve, between serum allopregnanolone concentration and adverse mood is observed in postmenopausal women treated with progesterone. Furthermore, the addition of low-dose progesterone to estradiol induces adverse mood in postmenopausal women, whereas higher doses and placebo have no mood-deteriorating effect.