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The Effect of Chronic Fluvoxamine Treatment on Overnight Melatonin Secretion in Medicated Chronic Schizophrenic Patients

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Overnight melatonin levels were measured in five male schizophrenic patients on steady antipsychotic treatment following the addition of fluvoxamine. Melatonin secretion increased in the first week of treatment and progressively decreased after 3 weeks. The findings are consistent with the development of tolerance in the processes underlying melatonin secretion.

KEY WORDS — melatonin; schizophrenia; fluvoxamine; tolerance

INTRODUCTION

Melatonin, a pineal gland hormone closely linked to serotonin, has been increasingly investigated in psychiatric illness. It is released rhythmically, mainly at night, under the influence of the supra chiasmatic nucleus (central clock). Mechanisms controlling its production involve indoleamines, catecholamines, adrenergic receptors, cyclic-AMP, methylation, light sensitivity and central rhythm generating systems (Arendt, 1989).

Melatonin secretion is affected by antidepressants although the significance of this for treatment response is yet to be determined. MAO inhibitors generally increase melatonin production (Arendt, 1989). A single dose of desmethylimipramine, primarily a noradrenaline uptake inhibitor advanced the onset of melatonin secretion in normal subjects leading to a longer duration of secretion (Franey *et al*., 1986; Skene *et al*., 1994). A single dose of fluvoxamine, a serotonin reuptake blocker did not alter the timing but increased the amplitude and duration in healthy volunteers (Demisch *et al*., 1986; Skene *et al*., 1994). Chronic (3 week) treatment with DMI in depressed patients tended to increase the amplitude of secretion without any effect on the timing (Thomson *et al*., 1985) whereas in normal volunteers an initial increase was followed by a return to baseline values (Cowen *et al*., 1985) suggesting that normal and depressed persons may differ. Low nocturnal levels of melatonin have been reported in depression (Mendelewicz *et al*., 1979; Wetterberg *et al*., 1982; Claustrat *et al*., 1984; Beck-Friis *et al*., 1985) and chronic schizophrenia (Ferrier *et al*., 1982; Fanjet *et al*., 1989) although the results are conflicting and may be affected by nonspecific factors such as weight or medication (Ferrier *et al*., 1982; Beck-Friis *et al*., 1984; Sack and Lewy, 1986; Arendt, 1989). Robinson *et al*., (1991) found blunting of nocturnal melatonin secretion in schizophrenics compared to schizoaffective patients emphasizing that diagnostic heterogeneity can also be a confound. Recently we (Silver and Nassar, 1992; Silver *et al*., 1995a) demonstrated that the addition of fluvoxamine improved negative symptoms in schizophrenic patients treated with antipsychotics. In the course of investigations into potential mechanisms of this effect we (Silver *et al*., 1995b) examined the effect of chronic fluvoxamine treatment on melatonin secretion in 12 chronic schizophrenic patients. The study found that morning melatonin levels increased during the first 5 weeks of fluvoxamine treatment and then declined returning to pretreatment levels by 8 weeks (Silver *et al*., 1995b). This we interpreted as evidence of the development of tolerance. Since in that study only morning levels of melatonin were measured it was not possible to determine which parameters of the secretion curve were affected. The purpose of the current study was to repeat and extend the previous findings by examining the effect of

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chronic fluvoxamine treatment on the overnight secretion of melatonin.

METHODS

The subjects, all male inpatients who gave informed consent, were physically well and fulfilled DSM III R criteria for chronic schizophrenia. All showed prominent negative symptoms (a score of at least 'moderate' on one of the five global scales of the SANS (Andreasen, 1983) and were candidates for fluvoxamine augmentation treatment for these. They all received antipsychotics, including aliphatic and piperazine phenothiazines and butyrophenones (most received more than one type) and trihexyphenidyl. The dose was constant for at least 4 weeks prior to and remained unchanged during, the study. Fluvoxamine 100 mg was added to the treatment regime and maintained throughout. Clinical state was assessed every 1 to 2 weeks with appropriate rating instruments.

Overnight serial blood samples were taken pretreatment, and after 1, 3 and 5 weeks. Samples were collected via an indwelling intravenous needle kept open by an heparin lock at 20.00, 22.00, 24.00, 02.00 and 08.00 h. Care was taken to prevent exposure of the patient to light, and a low intensity red light was used during night-time blood collection. The study was conducted in the winter months from November to February.

Blood was centrifuged within an hour of collection, plasma collected and stored at -70°C until analysis. Melatonin was assayed using enzyme immunoassay (EIA) as described previously (Silver *et al.*, 1995b). Intra- and inter-assay coefficients of variability (CV%) were 10·5 per cent and <14·8 per cent respectively.

RESULTS

Five male patients mean age 22·8 (SD = 5·9, range 18–32) years were studied. All had high negative (SANS range at baseline 41–70) and low to moderate positive (SAPS range 0–16) symptom scores. The small numbers did not allow meaningful analysis of change in clinical symptoms during treatment. Mean melatonin values at baseline were 10·34 (SD = 8·78), 32·80 (SD = 33·15), 67·80 (SD = 33·54), 64·00 (SD = 43·91), and 19·76 (SD = 26·25) pg/ml at 20.00, 22.00, 24.00, 02.00 and 08.00 h respectively. At 5 weeks the corresponding values were 14·00 (SD = 14·78), 17·44 (SD = 10·50), 31·00 (SD = 11·83), 14·80 (SD = 11·88), 26·60 (SD = 15·29).

Figure 1 shows the melatonin levels during the weeks of treatment. Melatonin secretion increased in amplitude and amount in the first week of treatment and then progressively decreased. Visual inspection suggested a shift in phase toward a later peak (02.00 h) but the changes were small and not statistically significant. Secretion extended longer into the morning hours as treatment progressed.

Statistical analysis comparing melatonin concentrations at the various sampling times at each treatment week showed significant time effect at baseline (Kruskal–Wallis one-way ANOVA 26 cases, $\chi^2 = 13{\cdot}2$, $p = 0{\cdot}02$) and week 5 (Kruskal-Wallis one-way ANOVA 26 cases, $\chi^2 = 15{\cdot}15$, $p = 0{\cdot}01$) but not at weeks 1 and 3.

Melatonin levels at each sampling time were compared with those at comparable time at each treatment period using nonparametric ANOVA analysis for related measures (Friedman two-way ANOVA). Melatonin levels at 24.00 h at 0, 3 and 5 weeks (where complete data was available) showed a significant effect of time ($\chi^2 = 6{\cdot}7$, $df = 2$, $p = 0{\cdot}035$). A similar analysis including week 1 where data from one patient was missing, showed a near significant trend ($\chi^2 = 2$, $df = 3$, $p = 0{\cdot}098$).

Paired comparison analyses (Wilcoxon matched-pairs signed-ranks test) of melatonin levels collected at the same clock time during the various treatment weeks were also performed. Significant differences or trends were found between: week 0 versus week 5, $n = 5$, $p = 0.08$; week 1 versus week 3, $n = 4$, $p = 0.07$, week 1 versus week 5, $n = 4$, $p = 0.01$; and week 3 versus week 5, $n = 5$, $p = 0.08$ for samples taken at 22.00 h, and between week 0 versus week 5, $n = 5$, $p = 0.07$; week 1 versus week 5, $n = 4$, $p = 0.14$; week 3 versus week 5, $n = 5$, $p = 0.04$ for samples taken at 24.00 h. Other paired comparisons failed to reach statistical significance.

DISCUSSION

Melatonin secretion showed dynamic changes in the course of fluvoxamine treatment with an initial increase and then flattening of the secretion curve and progressive extension of secretion into the early morning hours during the 5-week period. This was consistent with findings of our earlier study (Silver *et al.*, 1995b). The current findings confirmed that morning levels increase in the first 5 weeks, and indicate that the increase is due to a phase shift with secretion extending into the early

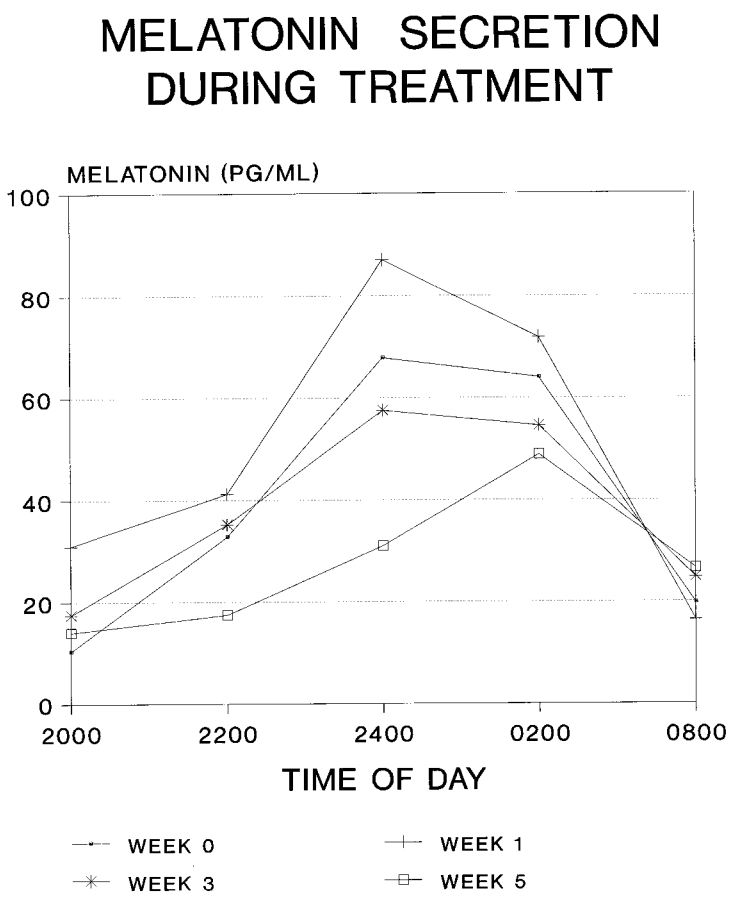

Figure 1. Overnight secretion of melatonin in the course of treatment with fluvoxamine in five schizophrenic patients on steady antipsychotic treatment

morning and occurs as the amplitude and amount of secretion declines. We did not have readings beyond 5 weeks in this study, but it is likely that after 5 weeks, the phase shift no longer compensates for the overall decline of secretion and morning levels decline as seen in our previous study (Silver *et al*., 1995b). Indeed we observed this in one patient who was followed for 8 weeks (unpublished data). The small number of patients and the frequency of sampling between 02.00 and 08.00 h did not allow an exact determination of a shift in the timing of peak secretion. Our findings are consistent with reports from studies of acute and chronic SSRI antidepressant administrations. Acute adminstration of fluvoxamine increased nocturnal plasma melatonin concentrations with high levels extending into the morning hours (Demisch *et al*., 1986; Skene *et al*., 1994). Chronic (6 week) treatment with fluoxetine resulted in a reduction in overnight secretion of melatonin in seasonal affective disorder patients and healthy controls (Childs *et al*., 1995).

The relationship of the changes in melatonin secretion to clinical response remains to be determined. In schizophrenics treated with add-on fluvoxamine, significant improvement in negative symptoms first appeared after 3–5 weeks (Silver and Nassar 1992). Since tolerance of melatonin secretion occurs between the first and third week of treatment it is possible that it bears some relationship to the therapeutic response. This requires further study.

The mechanism by which fluvoxamine affects melatonin secretion is not clear. It may act via serotonergic–adrenergic interaction affecting sensitivity of beta receptors (Demisch *et al*., 1987)

or via desensitization of somatodendritic 5HT1a autoreceptors (de Montigny *et al*., 1990; Li *et al*., 1993). Fluvoxamine can also affect the metabolism of melatonin (Skene *et al*., 1994), alter intracellular serotonin availability and increase the density of alpha-2 adrenoreceptors (Demisch *et al*., 1987). There is some evidence that fluvoxamine may also modify translation/transcription processes; Silver *et al*. (1995c) found that platelet MAO activity decreased after 5 week of fluvoxamine treatment in nine medicated schizophrenic patients.

The effect of concurrent antipsychotic medication on the findings is unclear. Fluvoxamine can increase blood levels of the antipsychotics (Daniel *et al*., 1994; Jerling *et al*., 1994 Hiemke *et al*., 1994). Phenothiazines can affect the metabolism of melatonin (Ozaki *et al*., 1976; Smith *et al*., 1979) as may fluvoxamine (Skene *et al*., 1994). However the biphasic nature of the response and the alterations in the pattern of secretion make a metabolic explanation unlikely. Although the number of patients in this study is small, the findings which confirm and extend those of the previous study, indicate that further investigation of the melatonin response may be useful in exploring the mechanisms of action of SSRI antidepressants and may provide a potential marker of treatment response.

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