Abstract  Rationale: The effects of antidepressants on sleep in depression have been extensively investigated, although to date there have been relatively few studies of newer drug classes such as specific serotonin reuptake inhibitors (SSRIs). All reported studies on SSRIs have been conducted in patients admitted to sleep laboratories and very few longitudinal studies have continued to measure sleep beyond 5 weeks of treatment. The growing trend towards outpatient and community care has highlighted the need for studies of sleep in depression in a more naturalistic setting, and during longer periods of treatment in line with recommended clinical practice. Objectives: To establish if the changes in sleep architecture and continuity described during early treatment with SSRIs persist after 3 months, to relate these changes to clinical state, and to establish whether home recordings would yield similar results to previous laboratory studies. Methods: We have recorded objective sleep parameters in 12 depressed patients before and during 12-week treatment with an SSRI, fluvoxamine. All the sleep recordings were performed in the patients’ own homes, using the Oxford Medilog system. Results: At 12 weeks, 7/12 patients had responded (HAM-D decreased by >50%). REM latency showed the expected increase early in treatment; this change was less obvious at weeks 3 and 12. Amount of REM sleep was decreased at day 2 and week 3, but returned to baseline by week 12. Slow wave sleep was slightly increased at day 2 and decreased at week 12. Of the sleep continuity measures, the only significant change was in sleep onset latency, which was increased at week 3; the other measures showed non-significant worsening at night 2 and week 3, but most were better than baseline by 12 weeks. Subjective sleep (the three sleep items on the HAM-D) showed a progressive improvement over time, especially in the responders. Conclusions: The effects of the SSRI fluvoxamine on objective sleep measures are in the direction predicted by its pharmacological actions and some persist for at least 12 weeks. In addition subjective appraisal of sleep is strongly affected by mood state. All patients found the home recording procedure acceptable and only minimally disruptive.

Key words  Sleep · Depression · Antidepressant · SSRIs

Introduction

Sleep changes in major depression are one of the few consistent and measurable biological effects of this disease. It is therefore important to study these changes and the effects of treatment on them. The most consistent anomalies have been described for many years, the most robust being rapid eye movement (REM) sleep advance – onset of REM sleep is earlier than in normal subjects and there is disruption of the normal preponderance of REM in the latter part of the night (for review, see Reynolds and Kupfer 1987). There is also a reduction of slow wave sleep (SWS), particularly in the first cycle. REM alterations were first described by Gresham et al. (1965) and since then have been found in depressed patients to varying degrees. Many measures of REM such as total duration in minutes over the night, length of each episode, number of episodes and eye movement during REM (REM activity) have been studied, but the most consistent abnormality found has been the time taken to enter the first episode of REM (REM onset latency, ROL). This is widely reported as being shortened in depression, particularly in patients with endogenous features (Hubain et al. 1995) and has been found to decrease with age and disease severity (Lauer et al. 1991). REM sleep abnormalities have been claimed to be not only a state marker for depression but also a trait marker,
as they have been found during remission in patients with recurrent depression (Giles et al. 1987) and have been proposed as a predictor of recurrence. REM abnormalities in first degree relatives of depressed patients have led to the proposal that these could be useful as vulnerability markers (Lauer et al. 1995).

Antidepressant drugs are known to have profound effects on sleep architecture and continuity both in volunteers and in depressed patients (Vogel et al. 1990; Sharpley and Cowen 1995). These effects are greatest and most consistent on REM sleep, and tend to be in the opposite direction to the sleep abnormalities found in major depression. Most sleep studies in both normal volunteers and patients have concentrated on the early stages of treatment. Fluvoxamine was shown by Berger et al. (1986) to suppress REM sleep in depressed patients early in treatment, and by Kupfer et al. (1991) to continue to do so up to 3 weeks. Some studies with the older tricyclic drugs (TCAs) have shown that the REM sleep changes produced early in treatment tend to decrease over the course of a few weeks (Dunleavy et al. 1972; Reynolds et al. 1991), interestingly, a similar time course to that of therapeutic effect. To date, there are few long-term studies with SSRIs; the longest study in depression reported at the time of this study has been 8 weeks (Rush et al. 1998). It seems that adaptive changes in REM sleep with these drugs may have a different time course to that seen with the traditional tricyclics which may reflect a different mechanism.

The time course of EEG sleep changes during antidepressant treatment is of interest in the light of this increasing knowledge of the mechanisms by which these drugs produce their antidepressant effects. The REM changes mentioned above are all present early in treatment with an antidepressant but the therapeutic effect does not usually appear for 2–3 weeks. Current practice is to treat patients with antidepressants for at least 6 months. It is therefore of interest to establish whether the early changes widely reported after SSRIs are still present after chronic treatment. Certainly in the case of the TCA imipramine, changes after 3 months and up to 3 years of treatment are reported to be minimal (Kupfer et al. 1994). Also of interest is the effect of long-term treatment with SSRIs on sleep continuity, since they are sleep-disturbing in the short term.

Nearly all the studies of sleep in depression and the effect of antidepressants have been carried out in sleep laboratories and hospitals, a large proportion in the United States. An interesting and important question is whether similar studies carried out with a home recording system in a UK outpatient population, normally treated in a primary care setting, would show similar changes. Studies in normal volunteers using this home recording technique have yielded robust results similar to those carried out in sleep laboratories (Friston et al. 1989; Sharpley et al. 1990), but long-term patient studies have not been reported. This is particularly relevant because of the growing trend towards the outpatient and community care of depression.

This study examines the sleep changes seen before and during long-term treatment with an SSRI, fluvoxamine, using an ambulatory recording system which measures these in patients’ own homes. Fluvoxamine is an effective antidepressant (Dominguez et al. 1985) of the SSRI type. It is a 2-aminooethylximethy aralkylketone that has potent effects on uptake of serotonin into platelets and rat brain synaptosomes without similar effects on noradrenaline uptake (Claassen et al. 1977). It has little effect at other receptors, apart from a weak antagonist action at \( \alpha_1 \) receptors.

We predicted that fluvoxamine would suppress REM sleep like other antidepressants and continue to do so without diminution at 3 months. There was no prediction of long-term sleep continuity changes, as the relationship between sleep improvement with response to treatment and sleep disturbance by SSRI was unclear.

Materials and methods

The study had the approval of the UBHT Ethics Committee and all patients gave written informed consent; the study was therefore performed in accordance with the ethical standards laid down in the declaration of Helsinki (1964).

Patients

Patients were recruited from a general practice and from a mood disorders clinic at the Bristol Royal Infirmary. All fulfilled DSM III-R criteria (APA 1987) for a major depressive episode with a Hamilton Depression Rating Scale (Hamilton 1960; HAM-D, 17 item) score of 17 or more; none had bipolar disorder and they were not actively suicidal. They were excluded if they had a sleep disorder other than insomnia secondary to depression and if there was a co-morbid severe mental illness; all had a normal and stable sleep-wake routine. No patients had taken any psychotropic medication for at least 2 weeks.

Twelve of the 16 patients recruited completed the study, eight females and 4 males, mean age 38.9, range 25–56. The four patients who withdrew included one who withdrew at day 4 because of side effects of gastrointestinal upset and insomnia, one who moved away from the area after 8 weeks, one who went back to work after 1 month and started shift work and so was excluded because his sleep pattern changed, and one who stopped taking the study medication for a short period just before the 3-month assessment without informing the investigators. Four of the completers had concurrent medical disorders that might have consequences for sleep; one migraine, one asthma, one ventricular aneurysm, one chronic back pain. None of these had attacks or worsening of symptoms on the recording nights.

Procedures

Patients were screened with a full medical and psychiatric history, and were rated using the HAM-D, the Montgomery Asberg Depression Rating Scale (MADRS) and the Clinical Global Impression (CGI). After informed consent was obtained a baseline EEG was performed using the home ambulatory monitoring system (Medilog). Subjects were visited in their homes during the evening and the recording equipment for electroencephalography, electrooculography and electromyography was attached, according to the standard sleep montage (Rechtschaffen and Kales 1968). They were then left to sleep normally at home. They were asked not to bath or shower with the equipment on but told that otherwise they could carry out their normal domestic routine; they were...