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Haloperidol Disrupts, Clozapine Reinstates the Circadian Rest–Activity Cycle in a Patient With Early-Onset Alzheimer Disease

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Summary: Measurement of the circadian rest-activity cycle in a patient with early-onset Alzheimer disease for 555 days revealed marked changes in the timing and amount of nocturnal activity. After neuroleptic medication was changed to haloperidol, the rest-activity cycle became completely arrhythmic for two months, concomitant with a marked worsening of cognitive state. Circadian integrity returned together with clinical improvement when the patient was subsequently treated with clozapine. This observation suggests that the known tendency for patients with Alzheimer disease to develop sleep-wake cycle disturbances may be aggravated by a classic neuroleptic; in contrast, the atypical neuroleptic clozapine may consolidate it. Similar observations in schizophrenic patients indicate that this chronobiological finding is drug- and not illness-related. **Key Words:** Circadian rhythms—Rest-activity cycle—Early-onset Alzheimer disease—Haloperidol—Clozapine.

Patients with Alzheimer disease (AD), in addition to experiencing progressive loss of cognitive function and change in personality, are particularly likely to show disturbances in the circadian rest-activity cycle (Aharon-Peretz et al., 1991; Okawa et al., 1991; Satlin et al., 1995; Van Someren et al., 1996; Ancoli-Israel et al., 1997; Mishima et al., 1997; Bliwise, 1999). These rhythm disturbances are often manifested as nocturnal restlessness and "sundowning." In this case study one of the drugs prescribed to treat nocturnal agitation is shown to actually worsen both the circadian rest-activity cycle and cognitive state.

CASE HISTORY

At 50 years of age, the patient contacted a memory clinic, where mild dementia was diagnosed, using the Mini-Mental-State Examination (MMSE) (Folstein et al., 1975), with a score of 26). At 54 years of age, the patient was hospitalized because of progressive mental decline to the point that she could no longer take care of herself (MMSE = 12). She was diagnosed as probable AD, early onset, according to NINCDS-ADRDA criteria (McKhann et al., 1984), but was otherwise healthy. Her ophthalmologic screening revealed no pathology except a red/green deficiency (Werth et al., 1999). Her MMSE score before discharge to a nursing home was 14; at the end of the study period, 15 months later, it was 9.

METHODS

The patient was asked to wear a small, noninvasive activity and light monitor (Actiwatch, Cambridge Neurotechnology Ltd., Cambridge, UK) on the nondominant wrist, and participation was permitted by her caregivers. Actimetry in patients with AD has been approved by the Ethical Committee of the Department of Medicine, University Hospital Basel. She was not included in any research or treatment protocol; medication was administered entirely according to clinical needs. At the end of the monitoring period, half-hourly salivary samples were

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collected under dim light in the evening and morning to measure the timing of melatonin secretion, and nocturnal urine was collected to assay the metabolite 6-sulphatoxymelatonin (Weber et al, 1997; Bühlmann Laboratories, Schönenbuch, Switzerland).

DATA PRESENTATION AND ANALYSES

The left panel of Figure 1 shows raw motor activity data in a very compressed double plot actigram (two consecutive days per horizontal line, consecutive days beneath one another), a form that aids perception of abnormal patterns. Sections A–F of the actigram were averaged over approximately 1 month to provide a mean 24-hour activity profile. This profile could be fitted into the timing of the nocturnal period between lights off and on averaged from the lux meter data, as an estimate of "time in bed." Sleepwatch software (Cambridge Neurotechnology Ltd.) was used to determine the time of "sleep onset," "wake-up time," and number and duration of nocturnal "wake bouts" (Table 1).

RESULTS

It should be emphasized that actimetry accompanied the clinical course, but was not used for clinical decision-

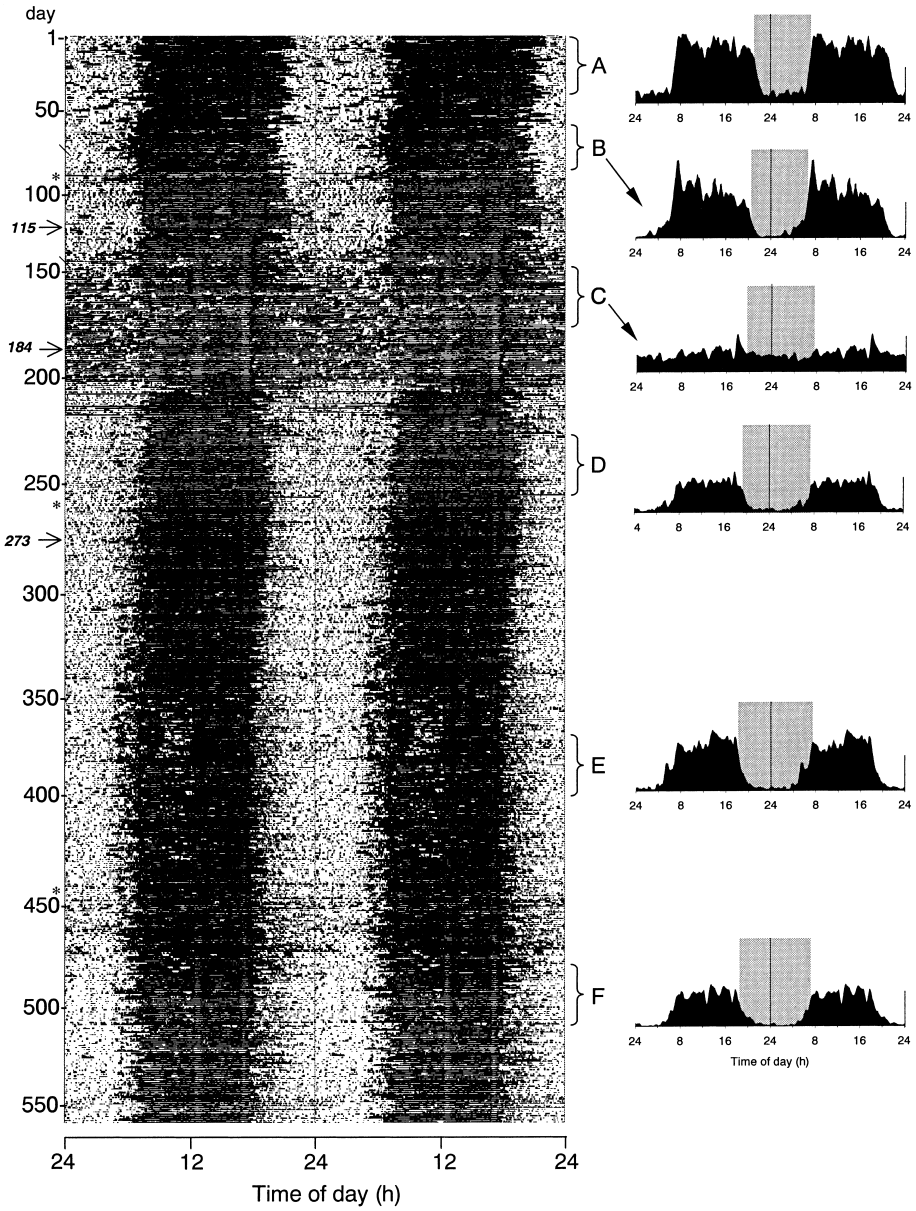

FIG. 1. Left: Motor activity is presented as a double-plotted actigram of the rest-activity cycle (1' bins, black bars = activity, maximum activity ≥500 counts). The data from days 1 and 2 are presented side by side (48 h) and beneath one another to facilitate visualization of the timing of activity onset and offset. Day of recording is on the ordinate: the arrows at day 115 = beginning of haloperidol treatment, 184 = beginning of clozapine treatment, 273 = increase of clozapine dose. The asterisks indicate a switch of monitors, \ = 8–10 days missing data. **Right:** Averaged activity profiles over 24-hours (0.5 hours running mean) double plotted for the respective sections of the actigram (number of days used: A = 35, B = 22, C = 32, D = 32, E = 31, F = 32). The nocturnal duration between lights-off and light-on (shaded area = "time in bed") was averaged from lux meter data over the same number of days. The units of activity counts cannot be directly compared across sections because of three monitor changes.

TABLE 1. *Medication and Sleepwatch analysis (mean values)*

Section of Figure 1.	Treatments, dosage	"Time in bed"	"Sleep onset latency"	"Sleep onset time"	"Wake-up time"	Number/duration of "wake bouts"
A	Risperidone, 2–3 mg/d Pipamperone, 20–30 mg/d	10 h 6 min	18 min	9:22 p.m.	7:03 a.m.	20/6 min
B	A + citalopram, 10 mg/d	10 h 7 min	8 min	8:33 p.m.	6:24 a.m.	19/4 min
C	Haloperidol, 40 mg/d	12 h 30 min	—	—	—	—
D	Clozapine, 50 mg/d Donapezil, 10 mg/d	12 h 13 min	33 min	7:58 p.m.	7:25 a.m.	28/3 min
E	Clozapine, 62.5 mg/d Donapezil, 10 mg/d	13 h 14 min	26 min	6:39 p.m.	7:09 a.m.	31/4 min
F	Clozapine, 62.5 mg/d Donapezil, 10 mg/d	12 h 38 min	11 min	6:50 p.m.	7:11 a.m.	23/3 min

Benzodiazepines and occasional treatments are not detailed. Measures are described in quotation marks to distinguish actimetry-derived from the conventional and more correct sleep-EEG-derived estimates.

making with respect to medication (details in Table 1). All analyses were post hoc, and thus this case history provides only a first piece of documentary evidence, under naturalistic conditions of hospital and nursing home practice, that certain drug treatments might be less than optimal. It is intended to raise awareness of the possibility of neuroleptic-induced, and not illness-related, disturbances of the circadian rest-activity cycle in patients with AD.

Visual inspection of Figure 1 shows that a dramatic change in the overall pattern emerged. At the beginning of the record the patient received risperidone and pipamperone. The rest-activity cycle was relatively well organized, but with some variability in its day-to-day timing, as well as bouts of nighttime activity (Fig. 1A). The antidepressant citalopram (10 mg/d) was added during the period represented by Figure 1B, which changed the wave form (a peak of morning activity, less afternoon activity, and less movement during the first part of the night) and shifted the rhythm to earlier. On day 115 the patient entered a nursing home and her neuroleptic medication was changed to haloperidol. About 10 days later the circadian rest-activity cycle began to disintegrate. Impressive but disturbing was the subsequent total arrhythmicity documented for over 2 months (Fig. 1C). Deterioration of cognitive state was progressive. Because of development of extrapyramidal symptoms, haloperidol dosage was gradually reduced, but without any improvement of circadian rest-activity cycle organization. Medication was then switched to clozapine on day 184, together with initiation of treatment with the anticholinesterase inhibitor donepezil. Two weeks later there was a sudden and rapid normalization of the rest-activity cycle, initiated by an apparent shift of wake-up time to earlier each day until it attained a new, stable timing (Fig. 1D). Orientation and memory also improved. Thereafter, these two medications were continued. When the clozapine dose was increased on day 273, early morning awakening was induced (Fig. 1E,1F). The early timing of sleep was matched by early timing of melatonin secretion: melatonin onset began at 6:40 p.m., and melatonin offset had already declined to baseline values at 6:45 a.m. Nocturnal excretion of the main melatonin metabolite was in the normal range. At the end of monitoring, the activities of daily living had improved, the patient recognized her caregivers, and appeared calmer and more content.

DISCUSSION

This is the first documentation of iatrogenic disturbances in the circadian rest-activity cycle in a patient with AD, and, should it be replicated, has widespread implications for strategies used in treating agitation and sleep-wake disturbances in AD. Complete arrhythmicity of the circadian rest-activity cycle occurred after treatment was changed to haloperidol, together with a massive deterioration in cognitive state. Both aspects were reversed after switching to the atypical neuroleptic clozapine. Donezepil was administered simultaneously, so that dual effects are possible. However, we have evidence from similar observations in patients with schizophrenia that this circadian-organizing effect may be clozapine-specific (Wirz-Justice et al., 1997; 2000). This also shifts the interpretation from a possible illness-related arrhythmicity to a drug-induced one. The sudden appearance of a completely arrhythmic pattern, together with a marked deterioration of cognitive state, was completely unexpected in this relatively young patient. In late-onset AD patients, rest-activity cycle disturbances usually develop over months and years (Witting et al., 1990; Van Someren et al., 1996; Werth et al., 1999).

It is known from sleep EEG recordings that clozapine has strong sleep-consolidating effects (Hinze-Selch et al., 1997), but up until now the circadian aspects of aug-

menting synchronization of the sleep-wake cycle have not been reported. The patient's sleep onset occurred as nocturnal melatonin rose, suggesting a phase advance of the circadian pacemaker. There are no studies reporting a phase advance in melatonin secretion related to clozapine treatment, although advanced phase of both sleep timing and melatonin secretion occurs with the aging process (Bliwise, 1999).

Chronobiologists posit that the integrity of the circadian rest-activity cycle has a functional correlate, in that correct timing is necessary for health. In patients with AD, the post mortem degree of degeneration of the biological clock in the suprachiasmatic nucleus (SCN) has been correlated with stage of dementia (Swaab et al., 1985), indicating an underlying process of decay in biological rhythm organization. Our finding adds another factor: a conventional neuroleptic given for the treatment of agitation in AD can exacerbate the disturbance, but an atypical neuroleptic can reverse it.

The finding that only haloperidol treatment, but not risperidone/pipamperone or clozapine, was associated with arrythmia argues for the importance of the serotonergic antagonist component in the circadian-stabilizing effect. Moreover, the better effect of clozapine may be related to its binding capacity to $5HT_7$ receptors, which are highly concentrated in the SCN itself (Lovenberg et al., 1993). In animal studies, $5HT_7$ receptors mediate serotonergic effects on the light sensitivity of the SCN. Clozapine enhances photic response (Ying and Rusak, 1997). The more sensitive to light, the better synchronized the rhythm and the earlier the phase: the early bedtime and morning awakening (and early phase position of the melatonin rhythm), which occurred after increasing the dose of clozapine, may indeed be a result of such augmented circadian photosensitivity.

This case study, by systematically following the circadian rest-activity cycle over a long period, points the way to integrating the 24-hour temporal dimension into the pharmacology of behavioral disturbances in AD, as recommended by McGaffigan and Bliwise (1997). Careful observation of the disturbed rest-activity cycle in individuals with AD may help dissect out illness-related degeneration and drug-related exacerbation. Certainly, further study of the putative correlation between strong circadian rest-activity cycle synchronization (as with clozapine) and cognitive state deserves attention, and comparison with other atypical and typical neuroleptics.

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