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Antiglucocorticoid Treatment Disrupts Endocrine Cycle and Nocturnal Sleep Pattern

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Summary. Mifepriston (RU 486) is a steroid antagonist which binds with high affinity to glucocorticoid receptors (GR), and also to progesterone receptors. The antiglucocorticoid action of Mifepriston in man has been demonstrated by blockade of the negative feedback action of endogenous cortisol and by antagonism of the effects of exogenously aministered dexamethasone. In the present study Mifepriston was administered to a normal male volunteer at 14.00 h and its effects on pituitary-adrenal activity and nocturnal sleep pattern were recorded. Mifepriston caused a large rise in plasma ACTH levels during the morning hours in comparison to untreated male control subjects. Plasma ACTH levels in the Mifepriston treated subject at 7.00 h were threefold greater than in the control subjects (104.4 pg/ml vs. 37.6 ± 13.9 pg/ml; $\bar{x} \pm$ SD). Subsequently the cortisol secretion was enhanced and the rise was advanced by about 60 minutes compared to controls. The main effects of Mifepriston on EEG sleep pattern were a dramatic disruption of sleep quality with a prolonged sleep onset latency, increased nocturnal awakenings and a considerable reduction of both slow wave sleep (SWS) and REM sleep. After Mifepriston, SWS was reduced by about 80% in comparison to placebo, and REM sleep was reduced by more than 50%. While the present data were collected from only a single subject the effects observed were so pronounced that tentative conclusions seem to be justified: The well-established pharmacological properties of Mifepriston as a glucocorticoid antagonist are reflected by its action on sleep physiology since it influences sleep in a direction opposite to that produced by cortisol. This observation further substantiates the view that changes in SWS and REM sleep may be mediated by GR effects.

Key words: Mifepriston – RU 486 – Cortisol – ACTH – sleep – antiglucocorticoids

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Introduction

Cortisol has a potent influence on several aspects of brain function. It coordinates circadian cycles in food intake, neuroendocrine secretion, and sleep (von Bardeleben et al., 1988, Born et al., 1987), and facilitates adaptation after stressful challenges. These effects result from binding to intracellular receptors and subsequent modulation of gene expression. Recent studies have shown that there are two types of corticosteroid receptors, i.e. the mineralocorticoid (MR) and the glucocorticoid (GR) receptor (de Kloet 1991). Since cortisol binds to both steroid receptor subtypes, the different effects mediated by MR and GR can only be identified by selective antagonists. Mifepriston (RU 486) is a selective GR antagonist, although it also binds to progesterone receptors. In man, the antiglucocorticoid action of Mifepriston has been demonstrated by its ability to antagonize the negative feedback action of cortisol and dexamethasone at the pituitary (Bertagna et al., 1984, Gaillard et al., 1984). Although several studies have described a reduction of SWS following MR antagonists (Born et al., 1991) the effects of GR antagonists on sleep architecture and concurrent endocrine effects have hitherto remained unknown. Here we report, for the first time, the effects of Mifepriston on the nocturnal sleep pattern and the concurrent alteration of nocturnal endocrine activity of the pituitary adrenocortical axis.

Methods

One healthy male volunteer, aged 26 years, was investigated on three consecutive days in our sleep research unit after a thorough medical examination including endocrine evaluation of thyroid and adrenocortical function and after written informed consent was obtained. The protocol was approved by our Ethics Committee for Human Experiments.

The first day served for habitutation to the experimental setting. On the second day at 14.00 h the volunteer received 2 placebo

tablets, and on the third day at 14.00 h two tablets containing 400 mg Mifepriston. On the second and third day at 13.00 h, prior to the Mifepriston and placebo treatment, an intravenous cannula was inserted into a forearm vein and connected with a tubing to the adjacent laboratory. The tubing was kept patent using 0.9% saline containing 400 IU/l of heparine. The volunteer remained isolated in a single bed room under video observation and was not allowed to sleep until 23.00 h. At 19.00 h a calorie- and electrolyte-balanced standard diet (4000 kJoules) in form of a beverage was provided. Water intake was restricted to 1.0 l from 13.00 h to 7.00 h next morning. Preparation for polygraphic sleep recordings was done between 22.0 h and 22.30 h. Lights were turned off at 23.00 h when the volunteer was allowed to sleep. Blood samples for measurement of plasma ACTH and plasma cortisol concentrations were drawn every 30 min via the tubing during the Mifepriston treatment, from 18.00 h until 7.00 h. Sleep was recorded between 23.00 h and 7.00 h on the second and third nights of the experiment. For determination of plasma cortisol levels a commercial radioimmunoassay kit (ICN Biomedicals Inc., Carson CA, USA) was employed. Plasma ACTH concentrations were determined by an immunoradiometric assay (Nichols Institute, San Juan Capistrano CA, USA). The sleep records were visually scored according to standard criteria (Rechtschaffen and Kales, 1968); definition of the EEG sleep parameters assessed are described in detail elsewhere (Lauer et al., 1991).

Results

Endocrine effects of Mifepriston treatment: In comparison to 15 male control subjects aged between 20 and 28 years, the cortisol secretion pattern after Mifepriston treatment showed a slight increase from 12 ng/ml to 86 ng/ml between 22.00 h and 23.00 h. This rise presumably resulted from the fixation of EEG electrodes. Interestingly, this cortisol surge was preceeded by only a minimal rise in ACTH levels. From 23.00 h until 03.00 h hormonal levels changed minimally (range 19–27 ng/ml plasma). Starting at 3.00 h cortisol levels showed a sharp rise. At 7.00 h plasma cortisol concentrations in the Mifepriston treated subject were higher than in the control subjects, reaching 186 ng/ml. The onset of the cortisol rise was advanced by 60 minutes in comparison to the control subjects (Fig. 1a).

Plasma ACTH levels between 18.00 h and 3.00 h were below 20 pg/ml, ranging from 7.5 to 14.9 pg/ml plasma.

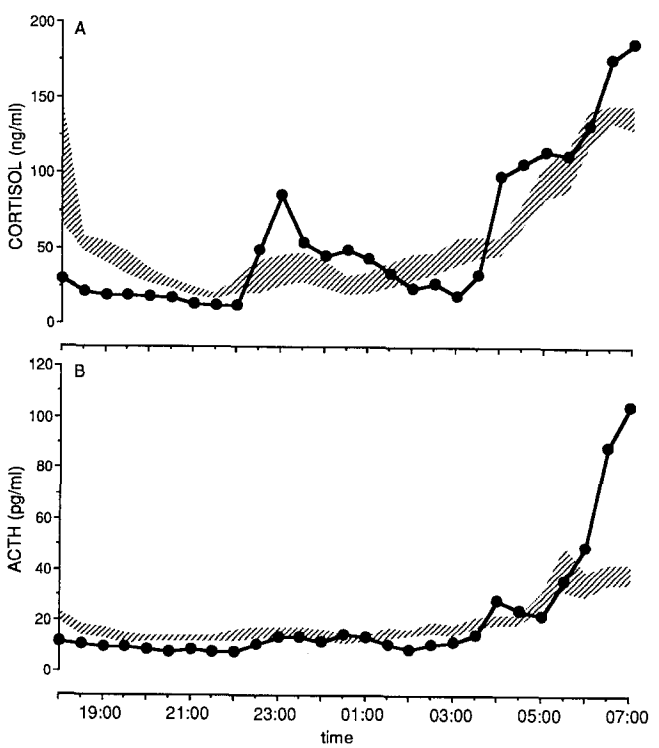

Fig. 1A, B. In **A** the filled circles indicate the plasma cortisol concentrations of the volunteer after pretreatment with Mifepriston at 14.00 h. The shaded area represents the mean ± SD plasma cortisol concentrations of 15 male control subjects without pretreatment. **B** shows the secretion of ACTH after Mifepriston treatment (filled circles) in comparison to the control subjects (shaded area)

Table 1. EEG sleep parameters during the placebo- and during the drug-night

	Placebo	Mifepriston
Sleep period time (min)	438.5	365.5
Sleep efficiency index (%)	93.0	62.5
Sleep onset latency (min)	20.5	108.0
Intermittent time awake (min)	12.5	72.0
Stage 1 sleep (min)	30.0	28.5
Stage 2 sleep (min)	237.0	199.0
Slow wave sleep (min)	49.0	9.5
stage 4 sleep (min)	44.0	6.5
stage 4 sleep (min)	5.0	3.0
REM sleep (min)	106.5	51.0
Mean REM density index	0.9	1.3
Stage 3 sleep latency (min)	20.0	22.5
Stage 4 sleep latency (min)	33.0	119.0
REM latency (min)	48.0	49.5
1st half of the night		
Before sleep onset		
Time awake (min)	16.5	105.5
Stage 1 sleep (min)	4.0	2.5
After sleep onset		
Time awake (min)	2.5	10.5
Movement time (min)	2.0	1.5
Stage 1 sleep (min)	10.0	5.5
Stage 2 sleep (min)	103.0	90.5
Slow wave sleep (min)	42.5	9.5
stage 3 sleep (min)	37.5	6.5
stage 4 sleep (min)	5.0	3.0
REM sleep (min)	49.0	11.0
REM density index	0.7	1.3
2nd half of the night		
Time awake (min)	10.0	61.5
Movement time (min)	1.5	4.0
Stage 1 sleep (min)	20.0	23.0
Stage 2 sleep (min)	134.0	108.5
Slow wave sleep (min)	6.5	0.0
stage 3 sleep (min)	6.5	0.0
stage 4 sleep (min)	0.0	0.0
REM sleep (min)	57.5	40.0
REM density index	1.1	1.3

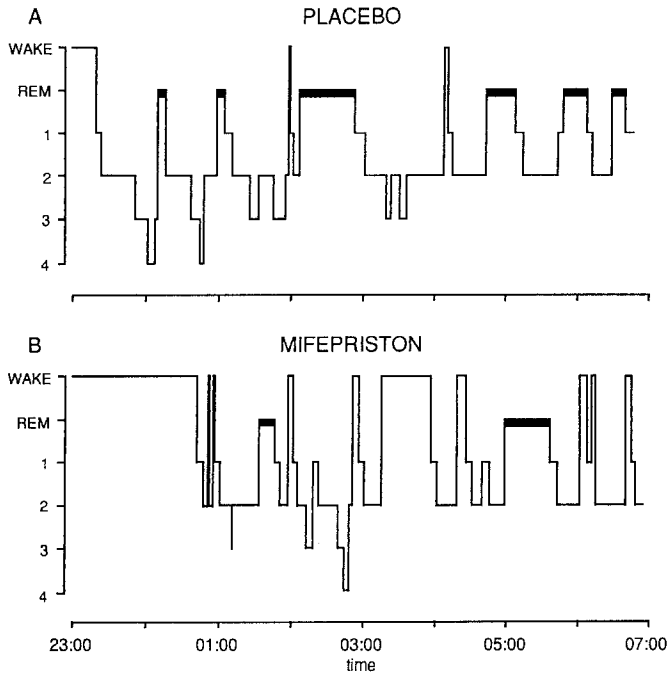

Fig. 2A, B. Figure 2 shows the polysomnogram of the night following placebo administration **A** in comparison to the night after administration of Mifepriston **B**. The detailed description is given in the 'results' section

Beginning at 3.30 h, first a slight increase, followed by a more pronounced increase in plasma ACTH levels occurred. The ACTH surge in the Mifepriston treated subject was advanced by about 90 min. After Mifepriston plasma ACTH concentrations at 7.00 h were 104.4 pg/ml plasma which, in comparison to the control subjects ($\bar{x} \pm$ SD, 37.6 ± 13.9 pg/ml plasma), represents a threefold increase (Fig. 1b).

Effects of Mifepriston on sleep architecture: The polysomnogram from the night following placebo administration (second night) revealed an undisturbed pattern (Table 1) congruent to those reported in healthy volunteers of similar age. A relatively early onset of REM sleep was observed. After administration of Mifepriston (third night) the sleep perid was obviously shorter, due to the fivefold increase of the sleep onset latency (Table 1, Fig. 2). Furthermore, there was a dramatic increase of intermittent time awake in parallel with more awakenings. Consequently, the sleep efficiency index dropped from 93% to 62.5%. Slow wave sleep (SWS) was nearly entirely suppressed and the first SWS period of a longer duration took place around 80 min after sleep onset.

Regarding REM sleep parameters there was a clear reduction of REM sleep mainly during the first half of both, the entire night and of the sleep period time (placebo: 49 min, Mifepristone: 11 min). The REM latency, on the other hand, remained at a constant level. The number of REM sleep periods decreased from 6 to 2. Finally, the density of rapid eye movements during REM sleep (REM density) was increased; this effect was most pronounced during the first half of the night and of the sleep period time, though REM sleep was reduced during these time periods.

Discussion

The current database is derived from one single subject and therefore any conclusion must be considered as being tentative. However, since the changes induced by Mifepriston were so pronounced, their discussion in the light of accumulated knowledge about the interaction between adrenosteroids and sleep physiology seems justified.

As expected, Mifepriston caused a large rise in plasma ACTH levels, followed by enhanced cortisol secretion. The main effects of Mifepriston on EEG sleep pattern were a pronounced decrease of sleep quality, including prolonged sleep onset latency and a considerably increased number of awakenings. Additionally, SWS and REM sleep were reduced, mainly during the first half of the night and of the sleep period time.

Administration of Mifepriston results in a pronounced activation of the HPA axis, which is regularly associated with a loss of negative feedback sensitivity e.g. to cortisol. The circadian pattern of HPA hormonal secretion generally remained intact, although we observed phase advances in the secretion of ACTH and cortisol as well as an augmentation of the basal secretory rates which is in keeping with other reports (Kling et al., 1989). The increased levels of ACTH and cortisol observed in this study could only have resulted from treatment with Mifepriston, a highly selective GR antagonist. Subsequently, MR mediated effects may become more apparent. This is important since MR are thought to mediate the tonic feedback control of the HPA system, and MR display circadian changes in the sensitivity to corticosteroids (Joëls and de Kloet, 1990, 1992). As demonstrated by Joëls and de Kloet, MR mediated effects increase the excitability of limbic neurons. Since Mifepriston has only a very weak affinity to MR (Clore et al., 1988), it becomes evident, that the hormonal effects of Mifepriston manifest first with an activated HPA system during the morning hours, where also GR should be occupied. Presumably, at the adrenal level, Mifepriston has no effect on release and biosynthesis of steroids, hence, the receptor antagonistic effect must be related either to pituitary or suprapituitary targets.

In our healthy volunteer, the administration of Mifepriston resulted in a clearcut increase in intermittent wake time in parallel with a dramatic reduction of both, slow wave sleep and REM sleep. These alterations appeared predominantly during the first half of the sleep period. Since effects of Mifepriston on ACTH and corticosteroid levels were mainly confined to the second half of the night, no associations between the hormonal changes and sleep pattern changes can be drawn. Rather the EEG sleep findings have to be related to direct effects upon brain GR. Since peripherally administered cortisol, which binds to both, the MR and the GR, is known to increase SWS (von Bardeleben et al., 1988; Born et al., 1987), the respective receptor antagonists should act conversely. This assumption is supported by the present findings with Mifepriston and the recent study of Born et al. (1991), who administered the mineralocorticoid antagonist canrenoate and observed a reduction in SWS. These authors, however, concluded that SWS changes are mediated

by MR, while changes in REM sleep are related to GR. While the latter notion is in agreement with our findings, the demonstrated specificity of MR mediated effects for SWS changes has to be extended with our new observation of GR mediated effects upon SWS. Taken together, the results of the present investigation and of the study of Born et al. 1991, lead to the conclusion that REM sleep changes mainly involve GR, whereas changes in SWS are mediated by both, MR and GR.

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