
Author’s address: Dr. H. Cramer, Department of Neurology, University of Freiburg, Hansastr. 9, D-7800 Freiburg i.Br. (FRG)


Study of a New Benzodiazepine using Automatic Analysis of Sleep Records

J. M. Gaillard, P. Schultz and R. Tissot
Psychiatric Clinic of Bel-Air, University of Geneva, Geneva

Ro 5^4200 is a new benzodiazepine with marked hypnogenic properties.
A previous clinical trial showed that 2 mg of this substance are at least as potent as 10 mg of nitrazepam [Schuler et al., 1972]. The investigation of its effects on sleep organization is of great interest since some
Table I. Effect of Ro 5-4200 on some of the more important parameters of sleep in four normal subjects (mean ± SE)

Free Communications: H. Effects of Drugs in Man; Therapeutic Aspects 492

Gaillard Study of a New Benzodiazepine 493

patients treated with Ro 5-4200 reported an increase in dream recall, and other benzodiazepines (diazepam, nitrazepam) seem to be able, in certain patients, to increase paradoxical sleep [Tissot, 1965].

In the present experiment, all-night sleep records were obtained from four healthy noninsomniac male subjects (mean age 25.7 years). Each of them spent 6 nights in the laboratory: habituation night (not recorded), two baseline nights, Ro 5\(^{4200}\) (1) 2 mg, and (2) 6 mg and withdrawal night. In baseline and withdrawal nights the drug was replaced by a placebo so that the subject had to take each night three pills of similar appearance. In our recording procedure we used 3 EEG leads (bipolar, F4-C4, C3-P3, P4-02), and 1 EOG lead with electrodes placed at the external angle of each eye; we also recorded the submental EMG, the ECG and the ESG. These parameters were amplified by an EEG machine (Schwartz) and recorded on magnetic tape (Philips Analog 7, FM, 7 tracks) during the entire night. The next morning the tape was replayed 16 times faster and analyzed by an analog and digital system (SEN Electronique) and a small general purpose computer (NOVA, Data General). This system has been described elsewhere [Gaillard et al., 1971, 1972], so has the analysis procedure and the program used for the computer [Gaillard and Tissot, in press]. The procedure results in a minute-by-minute sleep stage diagnosis accompanied by numerical values for rapid (REM) and slow eye movements, muscle activity, heart and breathing rates. Thus, this system quickly furnishes reliable results easy to process for further statistical calculation.

The latter is made on the same computer using a program written in BASIC which calculates a t-value for paired small samples. Each drug night or withdrawal night is compared with baseline, and the mean across subjects of these differences is used for calculation of the t-value.

Table I shows the effect of administration of medium and high doses of Ro 5-4200 on the more important sleep parameters. It is evident that the organization of sleep is modified; the number of sleep cycles is decreased, especially with 6 mg of Ro 5-4200, and the mean cycle duration is markedly increased; particularly the first cycle is prolonged and this is related to an increase of REM sleep latency and a marked decrease of REM sleep time. Both REM sleep percentage and REM sleep latency return to control levels in the withdrawal night. In contrast, deep slow-wave sleep (stages 3 and 4)
which also is markedly decreased on drug nights decreases still further in the withdrawal night. Thus, the sleep profile is smoothed, showing little else but long stages 2 and paradoxical sleep. With the high dosage of Ro 5-4200 REM sleep is atypical; while the tonic components are present there is an almost complete disappearance of the phasic components. Body movements are markedly decreased in the whole sleep.

We also have recorded two insomniac patients under the same conditions. Both showed a reaction to Ro 5-4200 quite different from that of normal subjects. In control nights their sleep was poorly organized, with a too-low amount of REM sleep. In the drug nights, their sleep organization improved, REM sleep latency remained short and, especially for one of these patients, REM sleep increased markedly. He also had more deep slow-wave sleep than he had on control nights. This improvement is probably associated with the effect of this drug on phasic components of whole sleep (body movements) and REM sleep (eye movements).

In conclusion, though Ro 5-4200 seems to disturb the sleep of normal subjects, it has a regularizing effect on certain kinds of dyssomnia. Evidently it is not always possible to predict exactly the effect of a drug by studying a normal subject.

Another interesting finding is the dissociation occurring in the normal subject between REM sleep and slow-wave sleep. The former is strongly affected by the drug but returns quickly to control level after withdrawal, while the latter seems to be lowered for a much longer period.

References


Tissot, R.: The effect of certain drugs on the sleep cycle in man; in Akert, Bally and
Schade Sleep mechanisms, pp. 175-177 (Elsevier, Amsterdam 1965).

Author’s address: Dr. J. M. Gaillard, Psychiatric Clinic of Bel-Air, University of Geneva, CH-1200 Geneva (Switzerland)