*Sleep*
10(6):563–569, Raven Press, Ltd., New York


# Butoctamide Hydrogen Succinate and Intensive Learning Sessions: Effects on Night Sleep of Down's Syndrome Patients

G. L. Gigli, ‡J. C. Grubar, †R. M. Colognola, †M. T. Amata, †C. Pollicina, †R. Ferri, †S. A. Musumeci, and *P. Bergonzi

*Clinica Neurologica, Università di Roma II (Tor Vergata), and *Istituto di Neurologia, Università Cattolica del Sacro Cuore, Roma, and †Centro Studi e Ricerche "Oasi" per la Prevenzione del Ritardo Mentale, Troina, Italy; and ‡IUT "B", Université de Lille III, France.*

**Summary:** Mentally retarded children present a reduction in percentage of REM sleep and of oculomotor frequencies. These sleep patterns are probably relevant for their cognitive activities. The effects of butoctamide hydrogen succinate and intensive learning sessions on the night sleep of five Down's syndrome patients was studied by the authors. They found an increase in percentage of REM sleep after pharmacological treatment and an increase in oculomotor frequencies after learning sessions. The authors' hypotheses of REM sleep as a neurophysiological indicator of cerebral "plasticity" and of oculomotor frequencies as an indicator of "organization" abilities are discussed in this article. Pedagogical implications and therapeutical perspectives are also outlined. **Key Words:** Learning—Butoctamide hydrogen succinate—Down's syndrome—REM sleep—Oculomotor activity.

In the experimental animal it is apparent that intensive learning sessions are followed by a consistent increase in REM sleep in the hours following such sessions (1); this increase is time limited and is not accompanied by slow wave sleep (SWS) modifications. However, data for related humans is rather controversial (2). These effects of learning sessions are more evident in very young subjects (3) and in those with learning disabilities (4).

Mentally retarded (MR) subjects present a sleep pattern characterized by reduced percentage of REM sleep, increased percentage of undifferentiated sleep (US), and prolonged latency to the first REM period (5–8).

Pètre-Quadens (9) observed that the ratio (R) between high and low oculomotor frequencies, i.e., between the number of REMs separated by intervals <1 s and those by intervals ≤2 s, ($R = I < 1$ s/$I \geq 2$ s) is increased with aging. She considered R as the ratio of order to noise or non-organization to organization as related to learning abili-

Accepted for publication May 1987.
Address correspondence and reprint requests to Dr. G. L. Gigli at Clinica Neurologica, II Università di Roma (Tor Vergata), Via O. Raimondo, Roma, Italy.

ties. In normal subjects, a significant increase in R is reported after training (10). Grubar (8) observed a significantly reduced R during nocturnal sleep of MR children and also mentioned that, in the same subjects, R does not correlate with age.

Butoctamide hydrogen succinate (BAHS), a derivative of a bromine organic compound normally occurring in cerebrospinal fluid, has already shown ability to increase REM sleep in cats (11), in healthy young volunteers (12), in aged subjects (13), and in MR subjects (14). In light of this, it seemed interesting to determine the possible effects of BAHS and intensive learning sessions on nocturnal sleep of Down's syndrome (DS) patients.

## MATERIALS AND METHODS

We studied the effects of intensive learning sessions on an etiologically homogenous group of five institutionalized, young male DS subjects (aged 9.5 ± 2.7 years) treated with BAHS. Their diagnoses had been confirmed by karyotyping: four subjects were moderately retarded (IQ 40–54) and one was severely retarded (IQ 25–39). All five had been drug-free for more than 2 months before the experiment, and none of the five was affected by other medical conditions known to modify sleep patterns.

Informed consent was obtained from the children's parents. Experimental design is shown in Table 1. Each subject spent 12 nights in the laboratory during an experiment which spanned 30 days.

During the nights preceded by drug administration (nights 4, 5, 26, and 27), subjects received 600 mg of BAHS p.o. 1 h before lights-out. Intensive learning sessions were held on days 26 and 27. The sessions were always administered by the same trained child psychologist. Each session was divided into 2 periods of 3 h each during which time a didactic program was used. The program was built so as to offer the children the logical relationships between the different steps proposed (highly organized and structured materials). The program included a series of 20 activities dealing with psychomotor and cognitive tests (Table 2). The subjects' performances were not considered because they were not pertinent for this experiment.

The learning sessions were administered concomitantly with the drug administration, in consideration of the hypothesis that even "organized" material could not be integrated by MR subjects without an increased ability to process and retain informa-

TABLE 1. *Experimental design*

| Stage | Nights |
|---|---|
| Adaptation | 1 |
| Recording: Base | 2–3 |
| Recording: BAHS | 4–5 |
| Wash-out | 6–7 |
| Recording: Rebound | 8–9 |
| Wash-out | 10–23 |
| Adaptation | 24–25 |
| Recording: BAHS and Learning | 26–27 |
| Wash-out | 28–29 |
| Recording: Rebound | 30 |

30-day experiment: 12 nights in the laboratory—3 were for adaptation, 9 for actual polygraphic recordings.

TABLE 2. *Activities presented to children during intensive learning sessions*

| | Learning activity | Task description |
|---|---|---|
| (1) | Auditory perception | Mnemonic differentiation of auditory stimuli |
| (2.3) | Seriation | Color and form alternation |
| (4) | Motor learning | Visual-motor coordination |
| (5.6) | Sequential perception | Object arrangement according to size and to length |
| (7.8) | Motor learning | Balance walking, manual dexterity |
| (9) | Associative recall | Object pairing by association |
| (10) | Imitation | Imitation of body postures |
| (11) | Maze learning | Obstacle avoidance |
| (12) | Visual-motor learning | Shape fitting |
| (13) | Goal-directed behavior | Goal achievement by means of nonverbal cues |
| (14) | Visual perception | Graphic representation of geometrical figures |
| (15) | Spatial differentiation | Recognition of opposite spatial concepts |
| (16) | Operant learning | Motor response evoked by rewarding stimulus |
| (17) | Seriation | Geometrical shape alternation |
| (18) | Problem solving | Puzzle assembly |
| (19) | Tactile perception | Tactile recall of properties in objects |
| (20) | Anticipation | Adjustment to coming stimulus situation |

tion; we think this is achieved by increasing the percentage of REM sleep. Each learning session was followed by a recording night.

Recording sessions took place in a quiet, partially soundproofed, shielded laboratory, located in the same institution. Children came to the laboratory at their usual bedtime, accompanied by their familiar assistants. These assistants remained with them until the onset of sleep. Children slept ad libitum on a familiar bed with temperature and humidity kept constant at comfortable values. So as not to overlook possible nocturnal myoclonus or respiratory disturbances, the children were constantly under audio- and video-tape control. Additionally, subjects were polygraphically recorded on the adaptation night to screen for these disorders.

Silver-cup electrodes, filled with conductive jelly and fixed with collodion were used for electroencephalographic (EEG) montage. For electro-oculography (EOG) and electromylography (EMG), "pellet" adhesive electrodes were used to reduce trauma. Impendance was always kept below 5 K ohms. Montage comprised three EEG leads (fronto-temporal and temporo-occipital in the dominant hemisphere, and bioccipital), two EOG leads (both external canthi for horizontal eye movements and above and below dominant eye for vertical movements) and one EMG lead (chin).

Recordings were obtained by an Ahrend-van Gogh 16-channel polygraph and were scored according to Rechtschaffen and Kales (15) by an independent scorer, blind to subjects' experimental conditions to avoid scoring biases. Due to the difficulty of scoring, typical of MR sleep recordings, another stage was considered, called undifferentiated sleep (US), according to the criteria of Lairy et al. (16). This stage has already been used in sleep scoring of MR by Pètre-Quadens (17) and by Grubar (8). In order to determine the ratio between high and low oculomotor frequencies proposed by Pètre-Quadens (9), only the horizontal REMs with an amplitude of at least 100 μV were calculated.

Due to the small sample size, non-parametric statistics (Wilcoxon's rank sum test) were used to evaluate results (18). During the 30-day experiment, routine hematochemical and urinary analyses were carried out to screen possible undesired side ef-

fects of BAHS, and scrupulous general and neurological physical examinations were performed.

## RESULTS

No undesired side effects were observed. Results are shown in Tables 3 and 4. The major effects produced by administration of BAHS in comparison with base nights are the significant reduction of US percentage and of latency to the first REM period together with a concomitant increase in percentage of REM sleep. Oculomotor frequencies ratio R was not modified by the drug. The drug appears to produce a certain hypnotic effect, as evidenced by the increase in SPT.

The comparison between nights preceded by the administration of BAHS alone and those preceded by both BAHS and intensive learning sessions reveals, first, a certain arousal effect of the 6 h of instruction [reduced total sleep time (TST), increased waking after sleep onset (WASO), percentage of stage 1 sleep, and number of awakenings (NW)]. It is important to note that the percentage of REM sleep is not significantly affected, although it is possible to observe a significant increase of the oculomotor frequencies ratio R. Data coming from the last rebound night (night 30) show a complete return to baseline values.

## DISCUSSION

The characteristics of baseline nights seem to be in accordance with previous data on sleep patterns of retarded subjects (5–8,17,19–25). In this study, the administration of BAHS (Table 3) increased the percentage of REM sleep and decreased the percentage of US and latency of the first REM period. These results are consistent with the effects of BAHS reported in animals (11), in healthy volunteers (12), in aged subjects (13), and

TABLE 3. *Effects of butoctamide hydrogen-succinate on sleep parameters*

| | Baseline[a] (Nights 2–3) | | BAHS[a] (Nights 4–5) | | Rebound[a] (Nights 8–9) | | Significance[b] Baseline vs BAHS ($p <$) | Significance[b] Baseline vs Rebound ($p <$) |
|---|---|---|---|---|---|---|---|---|
| TIB (min) | 586 | (35.6) | 606 | (33.6) | 589 | (36.8) | NS | NS |
| SPT (min) | 566 | (28.0) | 593 | (35.5) | 583 | (35.0) | 0.05 | NS |
| TST (min) | 549 | (34.0) | 564 | (32.5) | 560 | (34.4) | NS | NS |
| WASO% | 4.4 | (1.7) | 5.4 | (3.8) | 3.9 | (2.4) | NS | NS |
| S1% | 5.4 | (3.7) | 3.4 | (1.9) | 1.9 | (2.0) | NS | 0.05 |
| S2% | 49.4 | (4.9) | 51.9 | (8.9) | 55.9 | (6.7) | NS | NS |
| S3 and S4% | 22.2 | (3.6) | 22.5 | (7.2) | 22.8 | (4.1) | NS | NS |
| REM% | 15.5 | (3.8) | 17.6 | (2.3) | 14.8 | (3.2) | 0.05 | NS |
| US% | 7.5 | (3.7) | 4.5 | (2.6) | 4.9 | (2.7) | 0.01 | 0.01 |
| SOL (min) | 11 | (12.8) | 10 | (9.5) | 6 | (4.7) | NS | 0.05 |
| FRL (min) | 206 | (53.5) | 146 | (26.9) | 198 | (45.6) | 0.01 | NS |
| NW | 9 | (3.7) | 9 | (5.8) | 7 | (5.3) | NS | NS |
| R | 0.970 | (0.460) | 0.950 | (0.280) | 0.980 | (0.391) | NS | NS |

TIB, time in bed; SPT, sleep period time (TIB − initial and final wakefulness); TST, total sleep time (SPT − WASO); WASO%, wakefulness after sleep onset as a percentage of SPT; S1, S2, S3, S4, REM%, stages of sleep as percent of TST; US%, undifferentiated sleep as percent of TST; SOL, sleep onset latency; FRL, first REM period latency; NW = number of awakenings during SPT; R = ratio of oculomotor frequencies (I $<$ 1 s/I $\geq$ 2 s).

[a] Values given as means (SD).

[b] By Wilcoxon's *t* test.

TABLE 4. *Effects of BAHS and learning on sleep parameters*[a]

| | BAHS (Nights 4–5) | | BAHS and learning (Nights 26–27) | | Rebound (Night 30) | | Significance[b] BAHS vs. BAHS and learning ($p <$) | Significance[b] BAHS vs. Rebound ($p <$) |
|---|---|---|---|---|---|---|---|---|
| TIB (min) | 606 | (33.6) | 599 | (47.4) | 581 | (30.3) | NS | NS |
| SPT (min) | 593 | (35.5) | 592 | (48.7) | 575 | (32.7) | NS | .05 |
| TST (min) | 564 | (32.5) | 532 | (75.4) | 538 | (48.0) | .05 | .05 |
| WASO% | 5.4 | (3.8) | 10.5 | (8.6) | 6.5 | (5.8) | .025 | NS |
| S1% | 3.4 | (1.9) | 6.2 | (4.4) | 4.9 | (5.7) | .05 | NS |
| S2% | 51.9 | (8.9) | 52.4 | (5.4) | 47.7 | (6.4) | NS | NS |
| S3 and S4% | 22.5 | (7.2) | 20.3 | (5.2) | 24.3 | (6.1) | NS | NS |
| REM% | 17.6 | (2.3) | 18.3 | (4.8) | 16.6 | (3.5) | NS | NS |
| US% | 4.5 | (2.6) | 3.6 | (1.3) | 5.8 | (2.5) | NS | NS |
| SOL (min) | 10 | (9.5) | 6 | (5.0) | 5 | (3.6) | .05 | .05 |
| FRL (min) | 146 | (26.9) | 174 | (53.9) | 195 | (34.5) | .05 | .025 |
| NW | 9 | (5.8) | 13 | (4.8) | 11 | (4.7) | .05 | NS |
| R | 0.950 | (0.280) | 1.048 | (0.367) | 0.922 | (0.349) | .05 | NS |

See Table 3 for definition of abbreviations.
[a] Values given in means (SD).
[b] By Wilcoxon's *t* test.

in MR children (14). On the other hand, this study did not find that BAHS had an effect on the oculomotor frequencies ratio.

From a pharmacological point of view, it is important to note that BAHS seemed to be involved in the metabolic processes of serotonin (26), which appears to play a role, even if controversial, in REM sleep onset and maintenance (27,28) and is deficient in the brains of DS subjects (29).

When the administration of BAHS followed the "organized" learning sessions (Table 4), it was also possible to observe a trend toward a better R, oculomotor index of "organization."

Apart from these data on REM sleep, and US and oculomotor activity, it must be noted that when comparing BAHS nights with BAHS and learning nights, a certain disturbance is produced on sleep in the night following intensive learning sessions [reduced TST and sleep onset latency (SOL), increased percentage of WASO, percentage of stage 1 sleep, and as well as latency to the first REM period]. This effect is probably due to a "hyperexcitability" produced in children by an excessive amount of stimulation.

It appears worthwhile to speculate on these data in order to interpret them from a more holistic point of view. REM sleep is considered a particular state during which information is processed, memorized, and organized. The percentage of REM sleep seems to follow the phylogenetic scale and the ontogenetic process. Several data, although controversial in humans, seem to indicate a possible modification in REM sleep characteristics depending on learning sessions. Whether an increase in the tonic or phasic components of REM sleep resulted could be dependent on the difficulty of the task proposed, on species and individual differences, and on the efficiency of the system; that is, on its ability to respond in a more economic (phasic) way (30).

It is probably easier to obtain an increase in oculomotor frequencies than an increase in the percentage of REM sleep. In fact, the former requires only a functional reorganization of the system, whereas the latter is more dependent on the structure of the

system. The REM sleep increase could be more easily achieved when the subject is younger (3,31), or it could arise when all the possible increase in oculomotor frequencies have been exploited (32). BAHS, by interfering with neurotransmitters involved in REM sleep onset and maintenance, might facilitate a neuronal reorganization.

The data herewith support the percentage of REM sleep in humans as an index of cerebral "plasticity" (reduced in elderly subjects and in retarded children) and the REM frequency ratio ($R = I < 1s / I \geq 2s$), an index of cerebral ability to organize information (a further handicap for MR children). Thus, these consistent results concerning sleep patterns of MR children should encourage educators and parents to allow these children a delayed wake-up time and should alert physicians to be careful with psychoactive drugs that reduce the amount of REM sleep, in order to prevent a further reduction of the children's already decreased "plasticity." Further studies on larger samples and in chronic situations are necessary (a) to confirm the importance of "organized" didactic programs in helping MR children to overcome their impaired ability to organize information, and (b) to determine the real effectiveness of drugs capable of increasing their ability to retain the "organized" information presented. We expect that BAHS will be one of these drugs.

**Acknowledgment:** We thank Dr. A. Sakuma and Lion Co. for their active support.

## REFERENCES

1. Leconte P, Hennevin E, Bloch V. Analyse des effets d'un apprentissage et de son niveau d'acquisition sur le sommeil paradoxal consécutif. *Brain Res* 1973;46:367–79.
2. MacGrath MJ, Cohen DB. REM sleep facilitation of adaptive behavior: a review of the literature. *Psychol Bull* 1978;85:24–57.
3. Paul K, Dittrichova J. Sleep patterns following learning in infants. In: Levin P, Koella W, eds. *Sleep 1974*. Basel: Karger, 1974:388–90.
4. Castaldo V. Effects of a training program on the REM sleep of mentally retarded. *Psychophysiology* 1972;9:140.
5. Castaldo V, Krynicki V. Sleep patterns and intelligence in functional mental retardation. *J Ment Defic Res* 1973;74:231–5.
6. Castaldo V, Krynicki V. Sleep and eye movement patterns in two groups of retardates. *Biol Psychiatry* 1974;6:295–9.
7. Fukuma E, Umezawa Y, Kobayashi K, Motoike M. Polygraphic study on the nocturnal sleep of children with Down's syndrome. *Folia Psychiatr Neurol Jpn* 1974;28:333–45.
8. Grubar JC. Sleep and mental deficiency. *Rev Electroencéphalogr Neurophysiol Clin* 1983;13:107–14.
9. Pètre-Quadens O. Physiologie du sommeil et environnement. *Totus Homo* 1980;12:14–22.
10. Spreux F, Lambert C, Chevalier B, Meriaux H, Freixa i Baque E, Grubar JC, Lancry A, Leconte P. Modifications des caractéristiques du sommeil paradoxal consécutif à un apprentissage chez l'homme. *Cah de Psychol Cognitive* 1982;2:327–34.
11. Torii S, Inubushi S, Sakuma A. Effects of related compounds of naturally occurring bromosubstance on the sleep-wakefulness cycle in the cat. In: Weitzman ED, ed, *Advances in sleep research*. New York: Spectrum, 1975:155–63.
12. Okudaira N, Torii S, Endo S. The effects of butoctamide hydrogen succinate on nocturnal sleep: all-night polygraphical studies. *Psychopharmacology* 1980;70:117–21.
13. Hayashi Y, Otomo E, Okudaira N. Drug increased REM sleep in aged subjects: Butoctamide Hydrogen Succinate (BAHS). *Psychopharmacology* 1982;77:367–70.
14. Grubar JC, Gigli GL, Colognola RM, Ferri R, Musumeci SA, Bergonzi P. Sleep in Down's Syndrome Children: Effects of Butoctamide Hydrogen Succinate (BAHS) administration. *Psychopharmacology* 1986;90:119–22.
15. Rechtschaffen A, Kales A. *A manual of standard terminology. Techniques and scoring system for sleep stages of human subjects*. Washington, DC: Public Health Service, US Government Printing Office. 1968.
16. Lairy GC, Barros-Ferreira M, Goldsteinas L. Données récentes sur la physiologie et la physiopathologie

de l'activité onirique. In: Gastaut H, et al., eds, *The abnormalities of sleep in man*. Bologna: Aulo Gaggi, 1967:275–83.
17. Pètre-Quadens O. Contribution à l'étude de la phase dite paradoxale du sommeil. *Acta Neurol Psychiatr Belgica* 1969;69:769–898.
18. Lehmann EL. *Non parametric statistical methods based on ranks*. San Francisco: Holden Day, 1975.
19. Pètre-Quadens O, Jouvet M. Paradoxical sleep in mental retardation. *J Neurol Sci* 1966;3:608–12.
20. Feinberg I. Eye movement activity during sleep and intellectual function in mental retardation. *Science* 1968;159:1256.
21. Feinberg I, Braun M, Schulman E. EEG sleep patterns in mental retardation. *Electroencephalogr Clin Neurophysiol* 1969;27:128–41.
22. Schmidt H, Kaelbling R, Alexander J. Sleep patterns in mental retardation: Mongoloids and monozygotic twins. *Psychophysiology* 1968;5:212.
23. Grubar JC. Sommeil paradoxal et débilité mentale. *Enfance* 1975;(3/4):383–92.
24. Grubar JC. Le sommeil paradoxal des débiles mentaux. *Enfance* 1978;(2/3):165–72.
25. Clausen J, Sersen E, Lidsky A. Sleep patterns in mental retardation. *Electroencephalogr Clin Neurophysiol* 1977;43:183–91.
26. Ichikawa A, Kaneko H, Mori Y, Tonita K. Release of serotonin from mast cells induced by *N*-(2-ethylhexyl)-3-hydroxybutyramide and catecholamine. *Biochemical Pharmacology* 1977;26:197–202.
27. Wyatt RJ, Zarcone V, Engelman K, Dement WC, Snyder F, Sjoerdsma A. Effects of 5-HTP on sleep of normal human subjects. *Electroencephalogr Clin Neurophysiol* 1971;30:505–9.
28. Guilleminault C, Baker TL. Sleep and electroencephalography: Points of interest and points of controversy. *J Clin Neurophysiol* 1984;1:275–91.
29. Pètre-Quadens O, De Lee C. Serotonin and 5-hydroxytryptophan in sleep and mental retardation. In: Boullin DJ, ed, *Serotonin in Mental Abnormalities*. London: Wiley & Sons, 1978:257–72.
30. Gigli GL, Colognola RM, Musumeci SA, Valente M, Ferri R, Pollicina C, Bergonzi P. Sonno, Apprendimento e funzioni intelletive: Revisione della letteratura ed ipotesi interpretative. *Arch Psicolog Neurol Psichiatr* 1985;46:285–304.
31. Mirmiran M, van den Dungen H, Hyling H. Sleep patterns during rearing under different environmental conditions in juvenile rats. *Brain Res* 1982;233:287–98.
32. Pètre-Quadens O, Green H. Eye movements during sleep in weightlessness. *Science* 1984;225:221–2.