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The effect of niaprazine on some common sleep disorders in children

A double-blind clinical trial by means of continuous home-videorecorded sleep

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Abstract. A placebo-controlled double-blind clinical trial on the effect of niaprazine on children with some common sleep disorders was carried out. Niaprazine at a daily dosage of 1 mg/kg body weight or placebo at random was administered to a selected group of 36 children (aged from 6 months to 6 years) suffering from frequent nighttime waking or inability to fall asleep. The effect of niaprazine (or placebo) on sleep disorders was studied by means of continuous home-videorecorded sleep before and after the trial. A reliable positive effect of niaprazine on the sleep disorders considered was found. No adverse side effects were observed. We conclude that niaprazine seems to represent an effective and safe drug for the therapy of frequent nighttime waking and inability to fall asleep.

Key words: Sleep disorders – Drug therapy – Home videorecording – Niaprazine – Insomnia

Sleep disorders are found most frequently in children and particularly in preschoolers. Their occurrence varies from 20% to 40% in various studies [4–6, 21]. Among the most common disturbances are frequent nighttime waking and bedtime difficulties such as inability to fall asleep [2, 12, 13, 21, 25].

According to several studies a "sleep medicine" had been prescribed for 7–15% of preschool children with sleep disorders [19, 23]. Ounsted and Simons reported that by the age of 18 months 25% of 153 firstborns had received a sedative at some time [19].

Reports of two double-blind cross-over trials of trimeprazine tartrate in 1- to 3-year olds waking 5 or more nights a weeks have recently been published. The conclusion of both studies is that this treatment is not curative, but could be useful for crisis relief [23]. Niaprazine (*N*-[3-[4-(*p*-fluorophenyl)-1-piperazinyl]-1-methylpropyl]-3 pyridinecarboxamide) is an antihistamine with marked sedative effects, probably due to a disruption of 5Ht-NA equilibrium as a result of specific depletion of brain catecholamines [16]. The pharmacological effect of niaprazine on sleep disorders in children has recently been shown [7, 9, 10, 14, 24]. These studies were based on observations made by the nurses when the children were hospitalized for other medical problems or on observations made by their parents.

The purpose of the present investigation was to ascertain the effect of niaprazine on some primary sleep disorders in children aged 6 months to 6 years. We aimed especially: (1) to study the efficacy of niaprazine on the most common sleep disorders not caused by medical conditions in preschool children such as nighttime waking and inability to fall asleep; (2) to carry out a placebo-controlled double-blind trial of niaprazine; (3) to study the effect of niaprazine by an objective method such as Continuous home-videorecorded sleep (CHVS); (4) to verify the tolerability of the medicine.

Materials and methods

This study is based upon the children admitted to the neurological department at the Institute of child Neuropsychiatry, University of Rome "La Sapienza", from 1 November 1988 to 30 September 1989. During this period we selected a group of 36 children, aged from 6 months to 6 years, suffering nightly or at least 4 times per week during the previous 4 weeks from frequent nighttime waking and/or an inability to fall asleep.

Further criteria for inclusion were: (1) normal general physical and neurological examinations; (2) normal intellectual development appraised by Brunet-Lézine and Stanford-Binet scales according to age; (3) no previous or concomitant pharmacological treatment for sleep disorders.

In order to exclude other associated pathology, blood tests (complete blood count, erythrocyte sedimentation rate azotemia, glycemia) and urine analysis were carried out. As a result 15 males and 21 females, aged from 6 months to 5.8 years (mean age: 2.4 years), were selected.

The children were videorecorded in their own homes using CHVS, which provides direct observations on sleeping children in their natural setting. To have uninterrupted all-night sleep recording we modified [18] the time-lapse videosystem for home-recorded

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Table 1. Parameters of sleep evaluation

Parameters		Score
1. Sleep latency	Less than 10 min	3
	Between 11 and 20 min	2
	Between 21 and 30 min	1
	Higher than 30 min	0
2. Bedtime habits	Falling asleep without parents' help within 15 min	3
	Falling asleep without parents' help within 30 min	2
	Falling asleep with parents' help within 15 min	1
	Falling asleep with parents' help within 30 min	0
3. Nighttime sleep motor activity	Rare	3
	For less than half the night	2
	For half the night or more	1
	Almost continuous	0
4. Nighttime quiet waking	0–1	3
	2	2
	3	1
	More than 3	0
5. Nighttime crying waking	0–1	3
	2	2
	3	1
	More than 3	0
6. Mean duration of nighttime waking	Up to 5 min	3
	Between 6 and 10 min	2
	Between 11 and 20 min	1
	More than 20 min	0
7. Falling asleep without parents' help after night waking	Always	3
	More than half the time	2
	Half the time or less	1
	Never	0
8. Falling asleep with parents' help after night waking	Never	3
	Less than half the time	2
	Half the time or more	1
	Always	0
9. Nighttime spent out of bed	0–5 min	3
	6–10 min	2
	11–20 min	1
	More than 20 min	0
10. Total sleep time	8 h or more	3
	6–8 h	2
	4–6 h	1
	Less than 4 h	0
Total score		

sleep by Anders [1, 2], which consists of a videotape camera (Ikegami model ICD-290) with a special tube sensitive to low-level illumination (3 lux); a VTR recorder (Hitachi VT-145E); a dark-room light source in a spectral range compatible with the videotube's sensitivity; a time-date generator that prints a continuous display of time and date on the tape; and a microphone placed near the bed.

The video equipment was taken to the home in the evening and set up in the room where the child usually slept in such a way that the place was not noticeably altered. The parents were told to behave as naturally as possible. After activating the system the experimenters left and returned the following morning to remove it. At that time the parents were interviewed to make certain the children had presented their usual sleep problems.

The videotapes were played back at normal speed. We rated them on the basis of ten parameters, directly and indirectly connected to sleep disorders considered (Table 1). We used four arbitrary scores from 0 (very bad or severe) to 3 (good or absent), the sum of which provided a sleep evaluation. We considered the sleep as: (1) *good* (total score ranging from 26 to 30); (2) *disturbed* (total score ranging from 20 to 30); or (3) *very disturbed* (total score lower than 20).

To ensure adequate inter-rater reliability of sleep scoring all night videotapes were evaluated by two raters, neither knowing the scoring of the other. Inter-rater reliability was 0.82.

We used the first videorecording to confirm the sleep disorders that the mother complained of, as a further criterion for inclusion in the study and as a base for evaluation of drug effects.

From the evening subsequent to the night recorded we started a double-blind treatment with niaprazine or placebo. We explained the purpose and procedures of the study to the parents, who then signed a consent form.

The trial drug niaprazine (tradename Nopron, Maggioni-Winthrop) and placebo (the latter containing only the inert excipients of the active product) had been prepared and packed by the manufacturer as a completely indistinguishable syrup. All the children were given at random a single dose of niaprazine or placebo 30 min before bedtime. Daily dosage of niaprazine was 1 mg/kg body weight, as suggested by the manufacturer.

After 7 days of treatment we carried out a second CHVS and rated as described before. For each child the total score of the second videorecording was compared to that of the first one. We rated the improvement of sleep as follows: (1) a considerable improvement from very disturbed to good; or (2) a slight improvement from very disturbed to disturbed and from disturbed to good. Mothers were asked if the child complained of any problems during the treatment in order to evaluate adverse effects.

Statistical analysis of the results was carried out by means of nonparametric tests (chi-square, Fisher's exact test). Only the sex, age, and physical data of both groups were evaluated by means of Student's *t*-test for independent samples.

Results

At the first videorecording, all the children had a total score of sleep evaluation lower than 20 (very disturbed sleep), except for 1 child who scored 25 (disturbed sleep).

The two groups of children, double blind treated, were homogeneous for age, sex, weight, an height. Any slight differences occurred by chance. We compared the total score of the second recording to the first one. Of the 18 children treated with niaprazine, 12 (66%) showed a considerable improvement, 5 (27.7%) a slight improvement, and only 1 child showed no improvement. The average total score of the group before treatment with niaprazine was 8.50 compared with 20.83 ($P<0.001$). After treatment no worsening of the child's condition was observed.

In the group treated with placebo only 1 child (5.5%) showed a considerable improvement of sleep, another child (5.5%) improved slightly, while in 15 cases (83.3%) we found no significant changes. The average total score of the group before the treatment with placebo was 9.72 and after treatment 10.22 ($P>0.5$) (Table 2).

In the group treated with niaprazine we found a statistically significant positive effect on all sleep parameters considered (Table 3). Conversely placebo had no statistically significant effect on the same parameters (Table 2).

Comparing the effects of niaprazine on sleep disorders to those of placebo (Table 4), we found statistially signif-

Table 2. Effect of placebo on sleep parameters – evaluation by means of home-videorecorded sleep in 18 children

Parameters	Before therapy (mean score)	After therapy (mean score)	Variance (%)	*P* value
1	0.94	1.00	5.88	>0.05
2	0.89	0.94	6.25	>0.05
3	1.78	1.72	−3.12	>0.05
4	2.00	2.00	0.00	–
5	0.56	0.89	60.00	>0.05
6	1.33	1.22	−8.33	>0.05
7	0.39	0.39	0.00	–
8	0.17	0.39	133.33	–
9	1.17	1.11	−4.76	>0.05
10	0.50	0.61	22.22	>0.05

Table 3. Effect of niaprazine on sleep parameters – evaluation by means of home-videorecorded sleep in 18 children

Parameters	Before therapy (mean score)	After therapy (mean score)	Variance (%)	*P* value
1	0.72	2.22	207.69	<0.001
2	0.28	1.28	360.00	<0.001
3	1.50	2.06	37.04	<0.003
4	1.94	2.94	51.43	<0.0038
5	1.33	2.61	95.83	<0.0017
6	1.50	2.83	88.89	<0.001
7	0.06	1.28	2200.00	<0.001
8	0.06	1.28	2200.00	<0.001
9	0.72	2.50	246.15	<0.001
10	0.33	1.67	400.00	<0.001

Table 4. Efficacy of niaprazine versus placebo on sleep parameters – statistically significant differences. NE, No estimate because of the slight number of differences from 0 ($n<5$)

Parameters	*P* value between the groups
1. Sleep latency	<0.001
2. Bedtime habits	<0.0067
3. Nighttime sleep motor activity	<0.0032
4. Nighttime quiet waking	<0.0032
5. Nighttime crying waking	<0.02
6. Mean duration of nighttime waking	<0.001
7. Falling asleep without parents' help	NE
8. Falling asleep with parents' help	NE
9. Nighttime spent out of bed	<0.001
10. Total sleep time	<0.001

icant differences regarding the following parameters: 1–6, 9, 10 and particularly on parameters 1 (sleep latency), 6 (mean duration of nighttime waking), 9 (time spent out of bed), and 10 (total sleep time). It was not possible to find any statistical significance concerning parameters 7 and 8 because of the slight number of differences found.

The results of the interviews with the mothers on the 7th day of therapy showed a total absence of side effects and therefore perfect tolerability of the drug.

Discussion

Primary sleep disorders appear to be very difficult to treat pharmacologically. Especially for children, it is particularly difficult to find effective drugs for sleep disorders that entail no problems with regard to safety and tolerability. Therefore, the use of niaprazine seems to be very interesting. This drug, even showing an antihistaminic effect, differs from other antihistamines, particularly because of its marked sedative properties. Its pharmacological and toxicological effects and its clinical activity have been largely proved [7, 9–11, 14–17, 20, 24]. These clinical trials, however, were performed on patients affected by sleep disorders secondary to several medical conditions or on children with no previous diagnostic investigations to exclude other associated pathology. We think it is therefore difficult to assess the results of these studies due to the interference of other pathologies and their treatment.

In order to study the effectiveness of niaprazine on primary sleep disorders, we stress the importance of selecting carefully a group that could be considered healthy, except for sleep disorders. Furthermore, we think it's important to utilize a correct method of sleep evaluation. Previous investigations were based on subjective observations made by parents or by nurses, who usually change from time to time during the child's hospitalization. In contrast, most objective data on nighttime sleep in children were obtained by means of polygraphic recordings which necessitated a laboratory setting. An increasing body of evidence suggests that, even in the very young child, sleep recording under such conditions is distorted due to the laboratory situation [20]. It is also difficult to convince parents of children suffering only from sleep disorders to have them hospitalized in a sleep laboratory for at least 3 nights. All these methods, therefore, present some inherent difficulties. We believe that CHVS is superior to other methods. In the present study using CHVS, we obtained direct observations on sleeping children in their natural setting before and after treatment. We consider our findings reliable because of the careful selection of the children and the use of CHVS as a means of evaluating sleep.

Our results provide strong arguments that niaprazine resulted in considerable improvement on all ten parameters considered. The score of all parameters considered appeared to increase in the children treated with niaprazine (Table 3), while negligible changes were found in the group receiving placebo (Table 2).

Comparison between the effect of niaprazine and placebo on sleep parameters showed a positive effect of the drug on eight of them. No estimate could be made for parameter 7 (falling asleep without parents' help after nighttime waking) and 8 (falling asleep with parents' help after nighttime waking) because of the slight differences. Parameters 1 (sleep latency) and 10 (total sleep time) improved considerably (Table 4). Using CHVS it was possible to illustrate a positive effect of niaprazine even on sleep parameters not usually considered, such as nighttime quiet waking and nighttime sleep motor activity. We believe that the study of the latter is very interest-

ing due to its proven close correlation with emotional tone [20]. This suggests that niaprazine possibly normalizes the emotional tone, therefore improving the quality of sleep.

Our study showed that 66% of the children treated with niaprazine considerably improved and 27% of them presented a slight improvement. The above-mentioned positive effect occurred in almost all cases (93%).

In conclusion, our results, obtained by means of an objective method of sleep evaluation, permit us to affirm that niaprazine represents an effective and safe drug, at least for short-term therapy of nighttime waking and bedtime difficulties in children.

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