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A combination of valerian and lemon balm is effective in the treatment of restlessness and dyssomnia in children

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Abstract

Efficacy and tolerability of a combined valerian/lemon balm preparation[1] were investigated in an open, multicentre study in children less than 12 years suffering from restlessness and nervous dyskoimesis. Patients were dosed individually by the investigators. In total, 918 children were evaluated for therapeutic efficacy and tolerability. A distinct and convincing reduction in severity was found for all symptoms in the investigators' and parents' ratings. The core symptoms dyssomnia and restlessness were reduced from "moderate/severe" to "mild" or "absent" in most of the patients. In total, 80.9% of the patients who suffered from dyssomnia experienced an improvement for this symptom and 70.4% of the patients with restlessness improved clearly. For the other listed symptoms the total improvement was 37.8% on average. Both, parents and investigators assessed efficacy as to be "very good" or "good" (60.5% and 67.7%, respectively). The tolerability of Euvegal® forte was considered as "good" (in 96.7% of the patients it was judged to be "very good" or "good"). No study medication-related adverse events occurred.

In conclusion, Euvegal® forte was effective in the treatment of younger children with restlessness and dyssomnia and it was very well tolerated.

Keywords: Lemon balm/valerian combination; Restlessness; Dyssomnia; Children

Introduction

Restlessness and nervous sleep disturbance (dyssomnia) are considered to be mental disturbances with predominantly somatic symptoms. These include jactitation, stuttering, refusal to eat, anorexia nervosa and bulimia nervosa (WHO, 1992).

General motor restlessness can arise temporarily or can be a personality characteristic which continues beyond childhood. Children suffering from this syndrome are unable to sit still and their hands are always "on move". Particularly in situations which demand discipline and attention (e.g. during school), many children show a continuous motor restlessness. If no other symptoms of an endogenous or psychotic disease are present and no neurological deficits can be found such behaviour is called hyperkinetic syndrome.

Dyssomnia in children is expressed as difficulties in falling asleep (dyskoimesis) or in sleeping through the night as dysphylaxia, pavor nocturnus and somnabulism. Such disturbances often are temporary and the incidence in children is about 30%.

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[1]Euvegal® forte, manufacturer Schwabe Pharmaceuticals, Karlsruhe, Germany. [1 Dragee contains 160 mg drug extract of Valerian roots (DEV 4–5:1, solvent for extr. 62% ethanol) and 80 mg drug extract of lemon balm (DEV 4–6:1, solvent for extr. 30%)].

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Phyto-pharmaceutical products play an important role in the treatment of nervous dyssomnia and pathological restlessness. The positive effects of valerian on sleep disturbances have been demonstrated in many clinical studies (Stevinson and Ernst, 2000). Even in patients who took benzodiazepines before, a significant better subjective sleep quality was reported (Dorn, 2000). Compared to oxazepam no differences in the efficacy were found for valerian, but the valerian product had a favourable adverse effect profile (Poyares et al., 2002). The combination of valerian and lemon balm was also studied to show positive effects on sleep disorders as well as on the mood (Dreßing et al., 1996; Cerny and Schmid, 1999). In a clinical study the effects of a valerian/melissa combination compared to benzodiazepines was studied in adults with sleep disorders and insomnia (Dreßing et al., 1992). The positive results of this combination were documented and no daytime sedation or rebound phenomena were noted. Unlike the benzodiazepines, which have numerous unpleasant side effects, valerian extracts and lemon balm show only very low toxicity (McGuffin et al., 1997). There are no interactions with other drugs, however, due to its sedative properties it should not be used with alcohol (Blumenthal, 1998).

In children, alternative therapies in the treatment of attention deficit hyperactivity disorder (ADHD) and dyssomnia are of common interest. As stated in Psychosocial Paediatrics Committee (2002) some therapies for children are available. Valerian and lemon balm are considered to be effective with only rare side effects, but only limited study data were published (Hintelmann, 2002).

The aim of this study was to investigate the efficacy and tolerability of a valerian/lemon balm combination in the treatment of restlessness and nervous dyskoimesis in children younger than 12 years.

Materials and methods

Children younger than 12 years, suffering from pathological restlessness and/or nervous dyskoimesis, were included in this open, multicentre postmarketing surveillance study. The patients were treated for at least 4 weeks (± 1 week). The dosage of Euvegal® forte was chosen by the investigator with a maximum of 2×2 tablets/day. Each tablet consisted of 160 mg valerian root dry extract (*Valeriana officinalis* L.) with a drug-extract ratio of 4–5:1 (extraction solvent ethanol 62% V/V) and 80 mg lemon balm leaf dry extract (*Melissa officinalis*) with a drug-extract ratio of 4–6:1 (extraction solvent ethanol 30% V/V). No other medication to treat restlessness and/or nervous dyskoimesis was permitted. The children's parents were fully informed about the study by the investigator.

On baseline the investigators documented the medical history, e.g. the known duration of the illness, previous medical treatments, concomitant illnesses and the diagnosis of the present illness. To analyse the patient's disease the investigator had to select from three diagnoses (restlessness, nervous dyskoimesis and other), with multiple answers being possible. In addition, the incidence and the severity of symptoms were documented. The distribution of the symptom occurrence was divided in 4 categories (from every day to several times a month), whereas the severity was categorized from absent (0) to very severe (4). The following symptoms were listed at both visits: ''restlessness'', ''dyssomnia'', ''physical weakness'', ''rapid fatigability'', ''lack of concentration'', ''hyperactivity'', ''aggressiveness'', ''lack of appetite'', ''excessive drowsiness'', ''listlessness/dejection'' or ''other''.

At the final visit the incidence and the severity of the symptoms were compared to the data of the baseline visit and the course of the illness was documented for all symptoms by the investigators and the parents with the same score from absent (0) to very severe (4). Additionally, the improvement of the disease as well as the efficacy of the study medication were analysed in different questionnaires [improvement score ranged from 1 (very good improvement) to 5 (deterioration), the efficacy score ranged from 1 (very good) to 5 (poor)].

The physicians were asked to assess the tolerability of Euvegal® forte by a tolerability score that ranged from ''very good''(1) to ''poor''(5).

Adverse events had to be documented during the whole study phase.

Results

Patients

For this study, 938 patients were recruited in 207 paediatric centres in Germany. A total of 918 patients were evaluated for efficacy since 17 patients violated severely the inclusion/exclusion criteria and 3 patients did not perform any post-baseline visit and thus were not eligible for evaluation.

There were 56.8% male and 43.2% female patients ($n = 914$) with an average age of 8.3 years. 21.6% of the patients were younger than 6 years.

According to the patients' medical history the children suffered from their symptoms with a mean of 10.5 months (SD = 15.4 months). For a total of 264 patients (28.8%) at least 1 previous herbal treatment therapy was reported, for 101 patients (11%) other sedative drugs were noted. All the remaining patients

(60.2%) had no medical therapy for the study indication before.

The mean duration for study participation was 31.9 days (SD = 12.1 days).

The mean dosage at study start was 3.5 tablets/day. The standard dosage (4 tablets/day) was chosen for 74.6% of the patients. In the course of the study the dosage was modified in 68 patients (7.4%).

Efficacy

The incidence of symptoms was recorded at both visits. At the baseline visit, 566 patients (61.7%) reported of symptoms that occurred every day, at the final visit only 115 patients (12.5%) suffered from dyssomnia or restlessness every day. On inclusion, 99.3% of patients suffered from typical symptoms at least once a week, whereas only 71.5% revealed such symptoms weekly at the end of the study.

The core symptoms restlessness and dyssomnia improved significantly during the study.

Table 1. Examination of the core symptoms "restlessness" and "dyssomnia" at the first and second consultations

Symptom	Restlessness				Dyssomnia			
	First visit		Second visit		First visit		Second visit	
	Pat.	%	Pat.	%	Pat.	%	Pat.	%
No data	8	0.9	8	0.9	4	0.4	6	0.6
Absent	100	10.9	272	29.6	57	6.2	273	29.7
Mild	166	18.1	418	45.5	92	10.0	430	46.8
Moderate	347	37.8	169	18.4	327	35.6	170	18.5
Severe	258	28.1	41	4.5	381	41.5	33	3.6
Very severe	39	4.3	10	1.1	57	6.21	6	0.7
Total	918	100	918	100	918	100	918	100

Restlessness changed from "moderate" and "severe" (65.9% in total) to "absent" and "mild" (75.2% in total), dyssomnia improved from "moderate" and "severe" (77.1% in total) to "absent" and "mild" (76.6% in total). Table 1 demonstrates the development of the core symptoms during the study.

During the study, the "improvement in total", which was defined as an improvement by at least 1 or 2 points of the symptom score, was judged to be 70.4% and 80.9% for restlessness and dyssomnia, respectively.

All the other documented symptoms as listed above, improved likewise. The highest effects of improvement were measured for "dyssomnia" and "others" with values above 80%.

To assess the subjective efficacy, the parents of the patients were asked to fill in a questionnaire with a 5-point scale ("very great improvement" (1) to "deterioration" (5)). The investigator had to assess the efficacy by a scale that ranged from "very good" (1) to "poor" (5). Both, the investigators' and the parents' impression of the therapeutic effect of Euvegal® forte was good (Fig. 1).

Subgroup analysis

In a subgroup analysis the results were evaluated with regard to the age of the patients. The infant group (<6 years, 198 patients) and the school children group (≥6 years, 719 patients) were compared with respect to the daily dosage and the effects of the medication on the symptoms of their illness.

A total of 581 (80%) of the school children took the maximum dosage of 2 × 2 tablets/day, 112 (15.5%) of them took 2 tablets/day (2 × 1 or 1 × 2). To 102 (51.5%) of the infants a daily dosage of 2 × 2 tablets was prescribed, and 61 (30.8%) took 2 tablets per day (1 × 2 or 2 × 1). The remaining patients received 1 or 3 tablets/day.

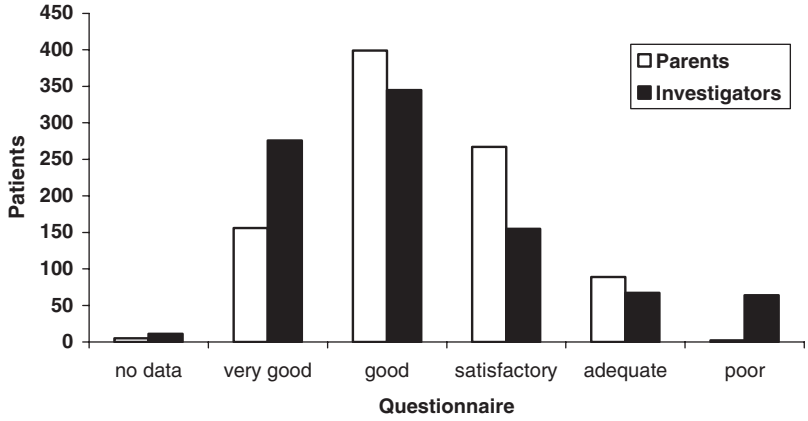

Fig. 1. Efficacy of a valerian/lemon balm combination in the treatment of restlessness and sleep disorders as assessed by the parents (white) and the physicians (black).

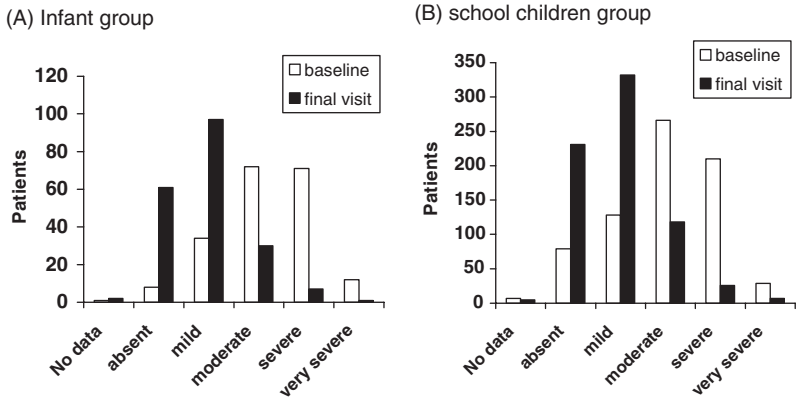

Fig. 2. Changes of the core symptom "restlessness" in the age groups.

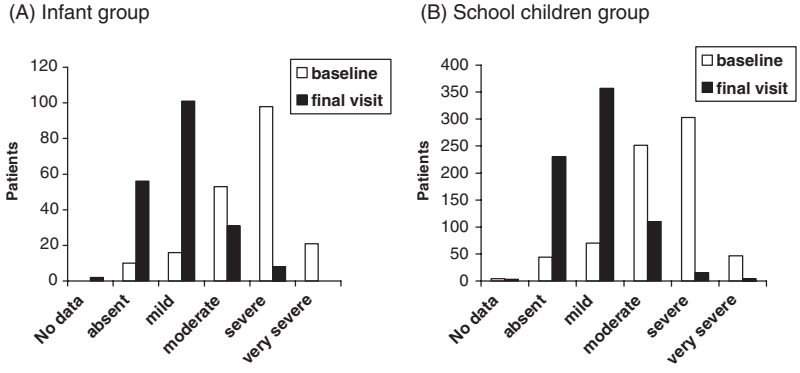

Fig. 3. Changes of the core symptom "dyssomnia" in the age groups.

A significant improvement of the core symptoms (restlessness and dyssomnia) was shown in both groups independently of age and dosage (Figs. 2 and 3).

The results demonstrate that both groups improved significantly with respect to the core symptoms restlessness and dyssomnia.

Safety

Tolerability

For 96.7% of the patients the tolerability was judged by the investigator to be "very good" or "good" (Table 2).

During this study, a total of 2 adverse events occurred. The first was acetonaemic vomiting, the second was an urinary tract infection. None of them were judged to be drug related by the investigators.

When the study was finished, 548 patients planned to continue the therapy with Euvegal® forte.

Discontinuation

In 157 of the 918 cases an early discontinuation was noted, for another 7 patients no data were available. For 142 of the dropouts the mean treatment duration was 22.3 days (SD 10.6 days), for the other 15 patients the data were missing. The reasons for discontinuation were selected by the investigators and are listed below in Table 3.

There was no case of "poor tolerability", and about half of the patients stopped treatment because of remission. Under "other" the following reasons were noted: no data (2), pharmaceutical form (14), lack of efficacy (12), compliance problems (9), admission to hospital (2, without any causal relationship to study drug), hyperactivity of the patient (1) and packet empty (1).

Table 2. Investigators' assessment of the tolerability of the valerian/lemon balm combination

Tolerability	Patient numbers	Percentage
Very good (1)	571	62.2
Good (2)	317	34.5
Satisfactory (3)	18	1.9
Adequate (4)	3	0.3
Poor (5)	1	0.1
No data	8	0.9
Total	918	100.00

Table 3. Reasons for early discontinuation during the study

Reason for discontinuation	Patients	Percentage
Treatment no longer needed	74	47.1
Parents request	64	40.8
Poor tolerability	0	0.00
Other	41	26.1
No reasons given	3	1.91
Total	182[a]	

[a]Multiple answers possible.

Discussion

In this multicentre observational study the herbal drug combination Euvegal® forte was effective in the treatment of children with restlessness and dyssomnia. The core symptoms of this common disease were evaluated in 918 children up to 12 years. During an average treatment period of 4 weeks with the valerian/lemon balm combination a fast and significant improvement of the disease in most of the patients was achieved.

The subgroup analysis showed that children of all evaluated age groups could benefit from this treatment. Since no study medication-related adverse events occurred, it can be stated that, together with former experiences (Dreßing et al., 1996; Cerny and Schmid, 1999), Euvegal® forte is a very well-tolerated medication. It is an important fact that the good therapeutic efficiency as well as the safety of the combination of valerian and lemon balm now could be shown in children up to 12 years, as already done in adult patients (Albrecht et al., 1995),

Due to the fact that synthetic psychotropic drugs bear a high risk of addiction or side effects, it should be forced on investigations of alternative therapies in the treatment of children. Different therapies are available and have been discussed before (Psychosocial Paediatrics Committee, 2002), but concrete comparisons of herbal and chemical drugs in the treatment of children are missing.

It should be the aim of further investigations to demonstrate the benefit of Euvegal® forte in clinical studies focussing on equivalence of this herbal combination with synthetic substances in children to reveal the risk–benefit ratio of the drugs.

In conclusion, it can be stated that Euvegal® forte might be an interesting alternative to chemical psychotropic drugs in the therapy of restlessness and dyssomnia in younger children.

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