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Modified-release methylphenidate in routine treatment

Efficacy and tolerability in a study in children and adolescents with ADHD (attention deficit hyperactivity syndrome)

Background and aims

The efficacy of methylphenidate (MPH) in children and adolescents with hyperkinetic disorders (HKD) resp. attention deficit hyperactivity disorder (ADHD) is very well documented in meta-analyses and systematic reviews of studies including several thousand children [1, 4, 10]. The active substance (MPH) reduces the core symptoms of attention deficit, hyperactivity and impulsivity with a response rate of approximately 75%.

The duration of optimal effect of MPH in its conventional immediate-release dosage form (MPH-IR) is usually 3 – 4 h. Longer-acting (sustained-release) preparations mean that it is possible to avoid additional doses of medication in the late morning at school for example, as this will often be forgotten and can also result in stigmatisation. Newer MPH preparations use a modified release formulation which combines an immediate-release and a sustained-release form of MPH [4]. The preparations available in Germany differ in the technique of sustained-release (e.g. gastric fluid resistant coating, specific osmotic release) and in the percentage of immediate-release MPH (MPH-IR). Whilst Concerta® contains 22% MPH-IR and achieves a duration of action of about 12 h, the proportion of MPH-IR in Equasym® retard is 30% and in Medikinet® retard and Ritalin® LA it is 50%. These differences in the pharmaceutical compositions of preparations are expressed in different pharmacokinetic and pharmacodynamics profiles; thus a higher proportion of immediate-release MPH in the same daily dosage shows greater effects in the morning [1, 8].

The efficacy of Medikinet® retard has been studied and confirmed in three multi-centre, randomised, double-blind, placebo-controlled studies [5, 6, 8, 9]. Such highly controlled studies are necessary in order to unequivocally prove the efficacy of a preparation. However the disadvantages of such studies are obvious: because of the inclusion and exclusion criteria for patient recruitment, they are usually very selective; moreover they can only enrol patients who agree to a large number of examinations, randomisation processes and potential placebo administration. Finally, the conditions under which the efficacy studies are performed often differ significantly from the everyday life situation of the patients. The diverse measures that serve to improve the internal validity of studies and thus ensure that the changes detected are in fact attributable to the treatment, at the same time reduce external validity and obtaining similar results in everyday clinical practice.

Non-interventional studies differ from efficacy studies in that there are considerably fewer experimental controls and the definition of the patient population is far less restrictive; this therefore permits therapeutic effects to be assessed under normal clinical conditions. When, as with this non-interventional study, a number of evaluators are enlisted to examine the effects, the quality of such 'naturalistic' open label studies is considerably improved, even though the evaluators do not have the status of fully independent observers.

The aim of the present study was to examine the effects of treatment with Medikinet® retard in routine clinical practice in patients who have received previous therapy, to examine the dose of MPH and patient compliance with the treatment.

Medikinet retard is identical to Medikinet XL or Medikinet MR; brand name suffix differs according to national regulations but represents the same medical preparation as modified release formulation.
The study was conducted with financial support from Medice Arzneimittel Pütter GmbH & Co.KG, Iserlohn.

Abstract

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Abstract

Background. This open label multi-centre non-interventional study examines the effectiveness and tolerability of a modified-release methylphenidate (MPH) preparation with a 50% immediate-release component (Medikinet® retard) in children and adolescents with attention deficit hyperactivity disorder (ADHD).

Methods. A total of 447 patients aged 6–17 years with ADHD and an indication for treatment with this preparation were included. Primary outcome measures were ADHD severity and side effects evaluated by the physicians and the parents at the start of the medication changeover and 4–6 weeks later.

Results. ADHD symptom severity declined significantly. Oppositional behavior and side effects as evaluated by the parents were also reduced.

Conclusions. This MPH preparation causes a further reduction of ADHD symptoms in hitherto sub-optimally treated patients. It is well tolerated and has been proven to be effective in clinical routine care.

Keywords
Hyperkinetic syndrome · ADHD · Pharmacotherapy · Methylphenidate · Open label study

Methods and Analysis

Children and adolescents in the age range of 6–17 years, who had been diagnosed with ADHD and in whom an indication for treatment with Medikinet® retard had been established, were enrolled in this non-interventional study pursuant to Section 4 (23) sentence 3 and Section 67 (6) AMG (German Medicines Act) [2]. Patients were excluded if they had any of the contraindications listed in the summary of product characteristics.

Two observation periods were scheduled, one at the start of the Medikinet® retard medication and one 4–6 weeks later. The parents were informed about data protection and data collection, and agreed to inclusion in this study.

The primary outcome measure (endpoint) for efficacy was an evaluation by the physician and the parents. The physician's task was to evaluate the severity of ADHD symptoms according to a global four-point scale [Clinical Global Impressions Scale (CGI-scale), 0: not at all, 1: mild, 2: quite severe, 3: very severe], based on the impressions conveyed by the parents. This evaluation was to be undertaken at the start of the study medication, retrospectively for the previous treatment or for the previous weeks (if no treatment was given), and again 4–6 weeks later when on treatment with Medikinet® retard. The physician also assessed compliance on the basis of a 6-point scale (1: very good to 6: unsatisfactory).

Parental evaluation was collected with the parental questionnaire ADHD daily profile sheet (ADHD-TAP-parents) at the same evaluation points. This newly developed questionnaire was specially designed to examine the effects of medication treatment and is part of the paediatric diagnosis system KIDS [7]. It is particularly useful for recording the duration of action of a given medication in the course of the day. It consists of two parts, in the first part, symptoms of ADHD (items 1–3) and aggressive-oppositional behaviour (items 4 and 5) are compiled, together with an overall assessment of the child's behavioural problems (item 6). The severity of these behavioural symptoms is assessed separately for four sections of daily life, based

Table 1 Daily dose (mg) of Medikinet® retard after medication switch according to age

Age group	Number of patients	Mean (mg)	Standard deviation (mg)	Minimum (mg)	Maximum (mg)
6–8 years	97	19.3	7.0	10.0	50.0
9–12 years	242	22.5	8.7	10.0	60.0
13–17 years	106	25.9	12.3	10.0	80.0
total	445	22.6	9.7	10.0	80.0

on a four-point response scale: morning (waking, dressing etc.), afternoon until approximately 16.00 hours (with lunch, homework), late afternoon until approximately 19.00 hours, and evening, including going to bed. The second part records potential adverse events of the medication based on 11 items. These characteristics are also assessed retrospectively for the previous week on the basis of a four-point response scale. The physicians were allowed to look at the questionnaires and use them to make their clinical evaluation and decisions.

Data processing was anonymised and the data analysis descriptive. Changes in the CGI scale were analysed statistically with the parameter-free Wilcoxon rank sum test. Interval level measurements were adopted for the changes to specific values in the ADHD-TAP and, despite the lack of a normal distribution, underwent parametric analysis with the t-Test for dependent samples. Cohen's d was used to calculate the descriptive measure for the severity of the changes; this relates the mean difference to its distribution. According to Cohen [3] values above 0.8 are interpreted as strong and values between 0.5 and 0.8 as medium effects.

Results

Sample

Data were collected from a total of 467 patients in 145 centres (paediatric and child and adolescent clinical practices). The selection of the centres was such that only clinical practices specialising in ADHD as identified by the sponsor's scientific ADHD field service were included. The project management made sure that these practices were spread evenly across Germany. One hundred and seven centres recorded up to 3 patients per centre, a further 36 centres recorded 4 to 8 patients, and 2 centres recorded 10 to 12 patients. A compensation of 50 EURO was paid for the time taken by the physician (approximately 40 min) to enter routinely collected data onto the observation sheets and to chart them accurately. Patients and parents did not receive compensation.

Out of the 467 patients 447 could be evaluated in terms of an 'intent-to-treat' analysis. The 20 patients who had to be excluded (because of a lack of information regarding age, sex, previous treatment with Medikinet® retard) were however included in the tolerability evaluation. 361 (81 %) of the patients were male. The average age was 10.7 years [standard deviation (SD) 2.5], ranging from 6–17 years. Half of the children and adolescents were at primary school (n=223; 50.1 %). Just under half of the patients (n=218; 48.8 %) had been diagnosed by the physician during routine clinical practice with straightforward attention deficit hyperactivity disorder (F90.0) according to the ICD-10 (International Classification of Diseases, 10th revision), and 43% (n=192) had hyperkinetic disorders which affected their social behaviour.

Previous treatments and medication switch

A total of 386 patients (86 %) had already received a stimulant (almost all MPH) before the switch in treatment, and almost 2/3 of patients had previously taken MPH-IR:

- 12.8 % (n=57) 1 x daily,
- 22.6 % (n=101) 2 x daily,
- 14.8 % (n=66) 3 x daily and
- 2.7 % (n=12) 4 x daily (the frequency of medication in 56 patients was not recorded).

10.1% of patients (n=45) had not received any previous medication; 65.3 % (n=292) switched to the preparation from one or repeated doses of immediate release MPH. Other previous medications were very rare (n=9, 2 %; n=11, 2.5 % no information).

46 % of the patients (n=202) had received additional non-medical treatment for ADHD in the past year. Altogether, 248 patients had at one time received non-medical treatments for ADHD, most frequently occupational therapy (72 patients), behavioural therapy (55 patients), psychotherapy (22 patients) and learning therapy (18 patients), and also training or counselling (18 patients). Before the medication switch, ADHD severity in 59.8 % of patients was assessed by the physician on the CGI scale as quite severe and in a further 11.5 % as very severe.

Patients who had previously received MPH treatment were administered 25.3 mg on average (SD 12.3 mg; range 5–80 mg) per day. The reason given most frequently by the physician for the medication switch, namely in 45 % of the patients (n=184) who had previously received medication, was that the patient was unwilling to take the second dose at school. Almost as frequently (43 %), the reason for the switch was that the second dose of the day was often forgotten. In 37 % of cases the physician stated that a single dose was insufficient, and in 23 % of cases the current sustained release preparation taken was judged to be sub-optimal (multiple answers possible).

Table 1 shows the daily dose of Medikinet® retard after the medication switch, differentiated according to age. With an average dose of 22.6 mg, the dosage for Medikinet® retard in the entire group (n=445) was somewhat below the dose for the previous treatment [AM (arithmetic mean) 25.3 mg, SD=12.3 in n=329 cases]. Based on body weight, less than 10 % of patients (n=39; 9.2 %) received a low dose [≤0.3 mg/kgBW (BW: body weight)], more than half (n=246; 58.1 %) an average dose (0.3–0.7 mg/kgBW) and almost a third (n=138; 32.6 %) a high dose (≥0.7 mg/kgBW).

In 57 % of cases there was improved compliance after the medication switch; no change was observed in 39 %, and compliance deteriorated in 4 %.

In 395 patients (88 %), the therapy with Medikinet® retard was continued after the study had finished. In 41 cases, the patient

Table 2 Severity of ADHD symptoms as evaluated by the physician (CGI)[a]

Sample	Number	Visit 1 on previous treatment Mean (Standard deviation) Median		Visit 2 on Medikinet® retard		Wilcoxontest statistic	effect size d
		Dose (mg)	Clinical evaluation	Dose (mg)	Clinical evaluation		
Total sample	432	22.24 (14.21) 20.00	1.82 (0.64) 2.00	22.01 (9.33) 20.00	1.09 (0.62) 1.00	14.68***	1.02
Partial sample after previous treatments[b]							
MPH-IR (total)	284	22.77 (10.93) 20.00	1.79 (0.63) 2.00	21.74 (8.95) 20.00	1.07 (0.60) 1.00	12.02***	1.07
1 x daily	57	14.61 (6.65) 15.00	1.75 (0.63) 2.00	18.25 (6.80) 20.00	1.04 (0.60) 1.00	5.40***	1.03
>1 x daily	179	25.47 (10.18) 25.00	1.82 (0.63) 2.00	22.47 (8.51) 20.00	1.13 (0.58) 1.00	9.48***	1.01
Concerta®	64	36.21 (13.31) 36.00	1.89 (0.59) 2.00	26.95 (11.29) 20.00	1.16 (0.74) 1.00	5.59***	0.99
Ritalin® SR/LA	26	27.50 (9.30) 30.00	1.38 (0.80) 1.00	23.46 (6.90) 20.00	1.27 (0.60) 1.00	0.76	0.14
No pharmacotherapy	46	0.00 (0.00) 0.00	2.15 (0.56) 2.00	16.74 (6.93) 20.00	1.09 (0.59) 1.00	5.66***	1.57

MPH-IR Methylphenidate with immediate- release, **LA** long-acting, **SR** sustained-release. [a] On previous treatment (Visit 1) and after switch to Medikinet® retard (Visit 2)
[b] Sums of partial samples due to missing values are sometimes smaller than total samples *p<0.05
***p<0.001

received an additional dose of MPH-IR (usually in the afternoon), and in 4 cases they received 2 doses of Medikinet® retard daily. The main reasons for non-continuation of the medication (11 %, n=53) were insufficient efficacy (n=21) and side effects (n=11).

Efficacy as evaluated by physicians

The physician evaluated the severity of ADHD symptoms on the CGI-scale at the first visit (before the medication switch) and the second visit (after the medication switch). There was a median of 40 days between the first dose of Medikinet® retard and the second visit. **Table 2** shows the results of these two evaluations in the total sample and in the partial samples with various previous treatments.

In the total sample, the physicians could establish a clear and statistically significant reduction in the severity of the globally evaluated ADHD symptoms. The effect size (Cohen's d [3]) indicated a major change between the two visits. In the partial samples, the greatest effect size (d=1.57) was found, as expected, in those patients who had received no previous medication. Similarly pronounced effects were evident in those patients who had been treated with immediate or sustained-release MPH, whereas the medication switch from Ritalin®-SR/LA (LA: long-acting, SR: sustained-release) showed the least additional improvement and was not statistically significant.

According to the global assessment by the physicians (CGI), in patients undergoing Medikinet® retard treatment 13.2 % (n=58) no longer displayed ADHD symptoms and a further 68.1 % (n=299) displayed only very slight ADHD symptoms, whilst the symptoms were still quite pronounced in 16.4 % (n=72) and very pronounced in 2.3 % (n=10). Overall, an improvement was observed in 282 (65 %) of all patients and no change in 133 (31 %). In 17 patients (4 %), the clinical findings had worsened. As expected, most patients (83 %) in the partial sample without medication treatment improved, in all other partial samples with previous medication improvements were observed in about 60-70 % of cases, except for previous treatment with Ritalin® SR/LA.

Parental evaluation

At both visits the parental questionnaire ADHD daily profile sheet was collected. In order to obtain an overall assessment of the ADHD symptoms and the oppositional-aggressive symptoms from the parents, the evaluations from the parents for the four different periods of the day (morning, afternoon until approximately 16.00 hours, late afternoon until approximately 19.00 hours, and evening) were averaged.

Parental evaluations were received at both visits for a total of 415 of the 447 patients (93 %). **Fig. 1** gives a graphical representation in effect size of the changes in ADHD symptoms and oppositional symptoms, as evaluated by parents, according to the various previous treatments. Clinically and statistically significant reductions (t-test for dependent samples) in the severity of ADHD symptoms and in oppositional symptoms as evaluated by parents were seen both in the total sample and in almost all the partial samples which were divided according to various previous treatments (the exception was previous treatment with Ritalin SR/LA). In contrast to the evaluation by physicians, the effect sizes indicate a somewhat weaker effect; they were however still in the mid to high range of mainly d≥0.5 (except Ritalin LA/SR). In the partial samples, again as expected, the greatest effect size was found in those patients who had not received any previous medication. Comparable results were demonstrated for ADHD symptoms and oppositional symptoms.

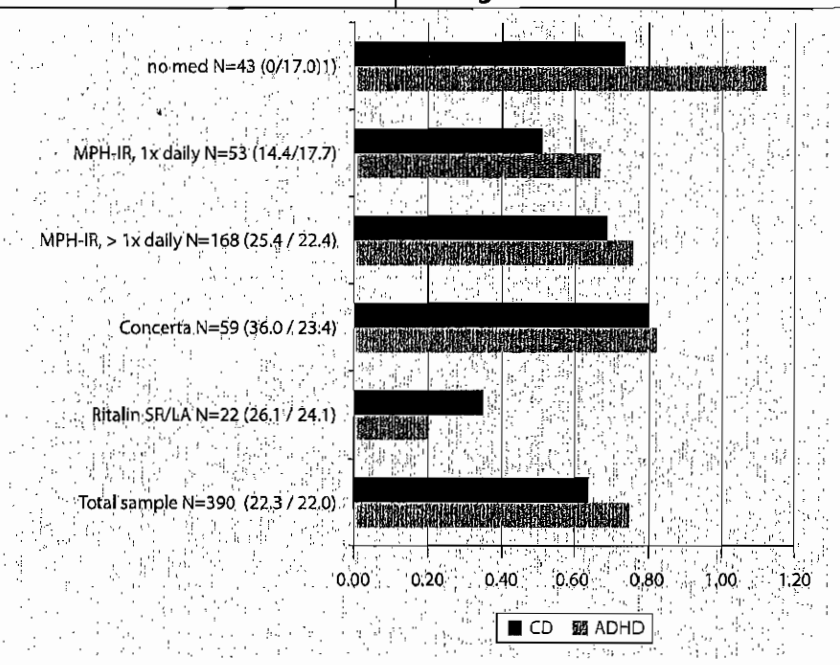

Fig. 1 ▲ Changes in ADHD symptoms (attention deficit hyperactivity disorder) and oppositional symptoms (CD conduct disorder) after previous treatment in effect size (Cohen's d), parental evaluation, ADHD-TAP (ADHD daily profile), average daily values, *values in brackets* daily dosage (mg) before and after the medication switch, *Concerta* Concerta®, *med* medication, *MPH-IR* methylphenidate immediate-release, *Ritalin SR/LA* Ritalin® SR/LA, *CD* conduct disorder

Tolerability

Adverse events (AEs) were recorded by the physicians in a total of 79 patients. In 34 patients (7.6 %), 43 AEs with Medikinet® retard were recorded. 36 AEs occurred in 27 patients (6.7 %) who had previously received ADHD treatment. The most frequent AEs were appetite disorders, head and stomach ache and sleeping disorders. 15 AEs that occurred on the previous medication and 13 on Medikinet® retard were described as severe. The physicians saw a definite or possible connection with 28 AEs on previous medication and in 33 AEs on Medikinet® retard. Serious AEs were not reported. Treatment was discontinued in consequence of previous medication in 5 cases and in consequence of Medikinet® retard in 10 cases.

The parents carried out evaluations of potential undesirable effects on a 4-point response scale based on 11 items on the ADHD-TAP at both measurement points. The specific value computed from these 11 items (sum of items/number of items) showed a statistically significant reduction ($t=12.09$, $p<0.0001$) in the total sample (n=402) from the previous treatment (AM=0.75; SD=0.46) to treatment on Medikinet® retard (AM=0.51; SD=0.39). The most frequent problems reported by the parents were connected with appetite, sleep and moody, irritable behaviour.

Discussion

Our research is the first non-interventional study to examine the efficacy of Medikinet® retard in a routine clinical practice setting. The overall evidence showed that Medikinet® retard was well tolerated in routine clinical practice, can be used effectively to treat the symptoms of ADHD, can improve compliance to medication and can contribute to a further improvement in symptoms in previously sub-optimally treated patients. It is important to note the following limitations of the study which must be borne in mind during interpretation of the results:

- The non-interventional study only applies to patients who were scheduled to have a switch or initiation of medication to Medikinet® retard, in most cases because the effects of the previous treatment or patient compliance were not satisfactory. It does not permit any assertions on the general efficacy of Medikinet® retard compared to alternative treatments. The analyses do however show that the symptomatology of patients whose previous treatment was unsatisfactory can improve after a medication switch to Medikinet® retard. This also explains why improved efficacy was achieved not only in patients who had not previously received medication and in patients who had received a single dose of MPH-IR, but also in those who had received repeated doses of MPH-IR and in patients who had previously taken Concerta®. The improved efficacy of Medikinet® retard compared to Concerta® may be explained by the higher proportion of immediately available methylphenidate in Medikinet® retard (50 %) compared with Concerta® (22 %). The relatively narrow superiority of Medikinet® retard compared with Ritalin® SR or Ritalin® LA can be explained if one considers that these patients presumably switched medication mainly because further health insurance funding for these preparations, which were not approved in Germany at the time of the study, was no longer possible. In these cases, the switch was not necessarily initiated because of sub-optimal efficacy. This is also evident from the fact that the ADHD symptoms in the group previously treated with Ritalin® SR/LA were significantly less pronounced during previous treatment than in the other groups. It must also be taken into account that the changes in the partial samples are to some extent based on low sample sizes.
- In an open, non-interventional study the influence of the expectations of the evaluators (physician, parents) cannot be monitored. However such effects are limited because of the inclusion of two evaluators. The fact that the effects as evaluated by physicians tended to be greater than those evaluated by parents could be due to the fact that physicians, who know more about the preparation, may have had greater expectations than the parents.

The principal efficacy of MPH was not examined in the study presented here; this has been investigated and demonstrated previously in randomised controlled studies. The non-interventional study presented here examines whether comparable effects can also be demonstrated in a normal patient population under routine clinical conditions using methods of quality assurance which could then be introduced into everyday clinical practice. That has been achieved with this study.

Conclusion for clinical practice

This study gives an insight into the clinical practice and effects of ADHD medication treatment in routine conditions and shows:

- **The average daily dose of 23 mg was in the moderate range. It decreased slightly in patients previously treated with MPH (from 25 mg to 23 mg).**
- **In patients who had received insufficient treatment with another MPH preparation, dose compliance on Medikinet® retard improved in 57% of cases.**
- **There was a reduction in symptoms as evaluated by both physicians and parents. According to the medical evaluation, 81% of patients had no or only few ADHD symptoms after the medication switch.**
- **In 79 patients, adverse events were recorded by the physician, and these events were described as severe in 15 cases of those on the previous medication and in 13 cases of those on Medikinet® retard. The most frequent AEs were appetite disorders, head and stomach ache and sleep disorders. In the parents' evaluation, a reduction in side effects was experienced on Medikinet® retard as compared with the previous treatment.**

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Conflict of interest. The corresponding author wishes to draw attention to the following connections: Prof. Döpfner is employed as a consultant to the following companies and receives research funding from these companies: Janssen-Cilag, Lilly, Medice, Novartis, Shire, UCB. Dr. Fischer is an employee of Medice. Ms Ose is participating in studies which are supported by the following companies: Medice, UCB

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