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Symptom control in children and adolescents with attention-deficit/hyperactivity disorder on switching from immediate-release MPH to OROS® MPH

Results of a 3-week open-label study

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Abstract *Aim* The aim of this study was to assess the impact of switching from immediate-release (IR) methylphenidate (MPH) to OROS® MPH (CONCERTA®), a once-daily long-acting MPH formulation, in children and adolescents with attention-deficit/hyperactivity disorder (ADHD). *Methods* Subjects with ADHD aged 6–16 (n = 105), who were stably maintained on their current IR MPH regimen (10–60 mg/day), were switched to 18, 36 or 54 mg OROS® MPH once daily for 21 days, depending on pre-study daily MPH dose. ADHD symptoms were assessed by parents, teachers and investigators. *Results* By Day 21, parent/caregiver IOWA Conners ratings had decreased from baseline by 2.7 points to 5.2 (I/O), and by 1.8 points to 5.0 (O/D). Teacher IOWA Conners ratings were maintained. Decreases in IOWA Conners ratings are indicative of ADHD symptom improvement. Approximately 75 % of parents and investigators rated therapy as good or excellent. OROS® MPH therapy was well tolerated. *Conclusions* Switching from IR MPH to OROS® MPH maintained and may have improved symptom control in children and adolescents with ADHD, during the course of this study. The changes in parent/caregiver IOWA Conners ratings suggest that OROS® MPH improves symptom control in the after-school period. This is consistent with the 12-h duration of action previously demonstrated for OROS® MPH.

Key words ADHD – CONCERTA® – long-acting – methylphenidate – OROS®

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) has a significant impact on individuals and their families, friends and society as a whole. Optimal management of the disorder aims to minimise not only the core symptoms, but also the associated impairments. Stimulants, and in particular, methylphenidate (MPH), are the recommended first-line pharmacotherapy for management of ADHD and can significantly reduce the core symptoms of the disorder in approximately 70 % of patients [1, 5]. The safety and efficacy of MPH in children has been extensively studied and has been summarised in a number of recent reviews and meta-analyses (e. g. 4, 7, 11). However, immediate-release stimulants require dosing 2–4 times a day, which is inconvenient for the patient, parents and teachers. This shortcoming has been overcome by the development of long-acting formulations that allow once-daily dosing. Current international guidelines for the management of ADHD thus recommend the use of long-acting formulations to avoid feelings of embarrassment associated with taking medication in front of one's peers and to reduce the risk of diversion [5]. The smoother pharmacokinetic profile of long-acting agents may also provide a more consistent medication effect. Once-daily dosing is also expected to improve compliance [13].

OROS® MPH (CONCERTA®) is a long-acting formulation of MPH which uses OROS® technology to produce an ascending MPH plasma profile with peak MPH concentrations occurring 6–8 h after administration [15]. The OROS® MPH tablet consists of an osmotically active drug core surrounded by a semi-permeable membrane and an overcoat of immediate-release MPH. In the gastrointestinal tract, the overcoat dissolves providing an immediate release of MPH. Further active drug is then released from the core at a uniquely patterned rate to produce sustained symptom control. OROS® MPH has been shown to improve behavioural and attentional symptoms of ADHD through a 12-h period [8, 15] and its efficacy has been shown to be comparable to that of immediate-release (IR) MPH dosed three times daily in three short-term, randomised, controlled studies in children [8, 15, 19]. In addition, the long-term safety and effectiveness of OROS® MPH has been demonstrated in two open-label studies lasting 9 months [12] and 24 months [16, 17]. These studies have all been performed in the USA where the diagnosis criteria differ somewhat from those generally used in Europe.

This European study, performed in centres in the UK and Germany, was devised to investigate the efficacy and tolerability of OROS® MPH when children and adolescents treated for ADHD were switched from IR MPH to the study medication. These children and adolescents were stable on their pre-study IR MPH regimen. A recommended algorithm was used to determine the OROS® MPH dose for each subject based on their pre-study IR MPH dose, and parent and teacher assessments were employed to assess the effect of switching to OROS® MPH on the core symptoms of ADHD. The effects of switching were also analysed by age, dose and ADHD subtype.

Methods

Study design

The efficacy and safety of OROS® MPH, in the clinical trial setting, has been demonstrated in three placebo/active-controlled double-blind studies. To validate the efficacy and tolerability of OROS® MPH in the European setting, a 'real-life' design was considered appropriate. This was a 21-day multicentre, open-label study involving six centres in the UK and five in Germany. Subjects received once-daily OROS® MPH and dose adjustment was allowed during the course of the study and was at the discretion of the investigator.

Following screening, eligible subjects were assigned to one of three OROS® MPH doses and received therapy for 21 days. Efficacy was assessed at baseline and on Day 21 by parents/caregivers, teachers and investigators, while possible effects on sleep, tics and appetite were reported by parents/caregivers on Days 7, 14 and 21. Parents also reported any adverse events at these study visits (Days 7, 14 and 21). Subjects who completed 21 days of therapy were eligible to continue treatment for up to 1 year.

The study was performed in accordance with the Declaration of Helsinki (revised version, October 2000), the Note for Guidance on Good Clinical Practice (July 1996), and applicable regulatory requirements. Prior to the commencement of the study, Independent Ethics Committees in each country reviewed the study protocol.

Subjects

The study aimed to enrol approximately 100 children aged 6–16 years with a DSM-IV diagnosis of ADHD of sufficient severity to require medication. All subjects had to have been receiving IR MPH at a daily dose of 10–60 mg for at least 4 weeks and been receiving their current dose for at least 3 weeks. In addition, subjects had to be able to comply with study visit schedules, to agree to take only the supplied study medication during the study, and parents/caregivers and teachers had to be willing to complete assessments. Subjects with known hypersensitivity to MPH, clinically significant gastrointestinal problems, glaucoma, a seizure or psychotic disorder, Tourette's syndrome, cardiovascular disease

including moderate to severe hypertension, hyper-excitability or agitated state, hyperthyroidism, depression, known or suspected substance abuse (current or past), and females who had reached menarche were excluded. Subjects receiving one or more of the following medications were also excluded: clonidine or other alpha-2 adrenergic receptor agonists, tricyclic antidepressants, theophylline, coumarin or anticonvulsants, or monoamine-oxidase inhibitors.

Dosing

Subjects were assigned to one of three OROS® MPH doses [18, 36 or 54 mg once daily (od)] based on their pre-study prescribed dose of immediate-release MPH.

Subjects receiving 5 mg IR MPH two or three times a day were assigned to OROS® MPH, 18 mg od; subjects receiving 10 mg IR MPH two (bid) or three times a day (tid) were assigned to OROS® MPH, 36 mg od; while subjects receiving 15 mg IR MPH two or three times a day or a total daily dose of > 45 mg-60 mg were assigned to OROS® MPH, 54 mg od. Clinical judgement was used to select the starting dose for subjects on other MPH regimens. Doses could be adjusted between these three levels at study visits on Days 7 and 14 on the basis of safety and efficacy observations by the investigator.

Efficacy assessments

The efficacy of therapy was assessed using two measures – the IOWA Conners rating scale and a Global Assessment of Effectiveness (GAE). The IOWA Conners scale [6] consists of two subsets of five items each: inattention/overactivity (I/O) and oppositional/defiance (O/D). Each item is rated on a four-point scale from 0 (not at all) to 3 (very much). Scores for each subset are summed separately (i. e. scores range from 0 to 15 for the I/O and O/D subsets), with lower scores indicating fewer ADHD symptoms. Normative data exist for the scale [10], which has shown discriminate validity [2] and is sensitive to medication effects [3, 9]. For the GAE, parents/caregivers, teachers and investigators rated treatment on a four-point scale (0 = poor, 1 = fair, 2 = good, 3 = excellent) in response to the question: "How would you rate the ability of this medication to control your child's/pupil's/patient's symptoms for ADHD?".

The primary measures of efficacy were parent/caregiver and teacher IOWA Conners I/O subscale ratings, assessed at baseline and Day 21, and parent/caregiver and teacher GAE ratings assessed on Day 21. Secondary efficacy measures were parent/caregiver and teacher IOWA Conners O/D subscale ratings, assessed at baseline and Day 21, and investigator GAE rating assessed on Day 21.

Adverse event assessments

Adverse events were recorded at each study visit and consisted of: recording spontaneous reports of adverse events; asking parents/caregivers to rate the quality of their child's sleep; asking parents/caregivers about their child's appetite over the past week; and asking parents/caregivers whether their child experienced tics during the past week. Sleep quality was rated on a four-point scale (poor, fair, good or excellent), as was appetite at baseline. At each subsequent study visit, parents/caregivers rated their child's appetite on a three-point scale (less than before, about the same as before, or greater than before) relative to the child's usual food intake before participating in this study. If the parent/caregiver reported tics, they were asked whether there was a change in severity or specificity during the past week.

Statistical methods

A sample size of approximately 100 patients was planned for this study on the basis of clinical considerations. The change from baseline in IOWA Conners scores over the course of the study was to be analysed using the paired t-test. Differences in treatment outcome between subgroups were to be described, but statistical tests were not performed as the small subject numbers in each subgroup would make quantitative conclusions difficult to draw.

All subjects who received study medication were included in both the efficacy and safety analyses (i. e. intent-to-treat (ITT) population). A last observation carried forward (LOCF) approach was used when analysing efficacy parameters.

Results

A total of 105 subjects enrolled in the study and received study medication (ITT population). The demographic and baseline characteristics of the study population are summarised in Table 1. In all, 17 % (n = 18) were adolescents (aged 13–16 years), while 45.7 % (n = 48) were children aged 10–12 years and 37.1 % (n = 39) were children aged 6–9 years. Approximately 40 % of subjects were receiving IR MPH at a dose of 10–20 mg/day, approximately 40 % were receiving IR MPH at a dose of 21–40 mg/day, and 14 % were receiving IR MPH at a dose of 41–60 mg/day. Subjects were receiving IR MPH on a bid or tid dosing regimen.

Of the 105 subjects, 99 (94.3 %) completed the 21-day study. The completion rate was similar across all three age groups (88.9 %–97.9 %). Eighty-nine patients continued with study treatment after this period. Reasons for not entering the follow-on study included lack of ef-

Table 1 Baseline demographics and characteristics of study population

	6–9 years n = 39	10–12 years n = 48	13–16 years n = 18	All subjects n = 105
% Male (n)	84.6 (33)	81.3 (39)	100 (18)	85.7 (90)
ADHD subtype, % (n)				
Combined	76.9 (30)	68.8 (33)	55.6 (10)	69.5 (73)
Inattentive	15.4 (6)	25.0 (12)	33.3 (6)	22.8 (24)
Hyperactive/impulsive	7.7 (3)	6.3 (3)	11.1 (2)	7.6 (8)
Mean parent/caregiver IOWA Conners I/O rating (SD)	7.8 (3.5)	7.7 (3.6)	7.7 (3.6)	7.8 (3.5)
Mean teacher IOWA Conners I/O rating (SD)	5.7 (3.1)	4.7 (2.9)	6.4 (3.7)	5.4 (3.2)
Mean parent/caregiver IOWA Conners O/D rating (SD)	7.3 (4.4)	6.4 (3.6)	6.6 (4.3)	6.8 (4.0)
Mean teacher IOWA Conners O/D rating (SD)	2.5 (2.9)	2.4 (2.6)	3.2 (3.4)	2.6 (2.9)
Pre-study daily IR MPH dose, % (n)				
10–20 mg	56.4 (22)	37.5 (18)	22.2 (4)	41.9 (44)
21–40 mg	38.5 (15)	52.0 (25)	33.3 (6)	43.8 (46)
41–60 mg	5.1 (2)	10.4 (5)	44.4 (8)	14.3 (15)

ficacy of the maximum dose (n = 8, 7.6 % of all subjects) – reported most frequently in the 10- to 12-year-olds (n = 6, 12.5 %) – and adverse events (n = 5, 4.8 %).

At the start of the study, 20 (19 %) subjects were assigned to the 18 mg dose, 59 (56.2 %) to the 36 mg dose and 26 (24.8 %) to the 54 mg dose. At the end of the 21-day study period, the dose distribution was similar although the percentage of subjects receiving the highest dose had increased to 33.7 % and there were slightly fewer subjects receiving the lower two doses (18 mg, 11.9 %; 36 mg, 54.4 %). In total, 27.6 % of subjects (n = 29) had their initial OROS® MPH dose adjusted in the course of the study.

Efficacy

At Day 21, IOWA Conners I/O ratings were 5.2 ± 3.4 for parents/caregivers and 5.7 ± 3.5 for teachers. Parent/caregiver IOWA Conners I/O and O/D ratings decreased from baseline, indicative of symptom improvement [change from baseline in IOWA Conners I/O, –2.7 ± 3.5; change from baseline in IOWA Conners O/D, –1.8 ± 3.7; for both parameters the change from baseline was statistically significant ($p < 0.001$)].

The decrease was somewhat greater for adolescents (compared with the younger two age groups) (Fig. 1) and similar for the three dose groups (Fig. 2). The decrease was somewhat greater for subjects with combined subtype ADHD compared with predominantly inattentive subtype ADHD (change from baseline in parent/caregiver IOWA Conners I/O: combined, –2.7 ± 3 vs. inattentive, –2.1 ± 3.6; change from baseline in parent/caregiver IOWA Conners O/D: combined, –1.8 ± 3.9 vs. inattentive, –1.3 ± 3.5). (Formal statistical comparisons between subgroups were not performed as the small subject numbers in each subgroup make quantitative conclusions difficult to draw.)

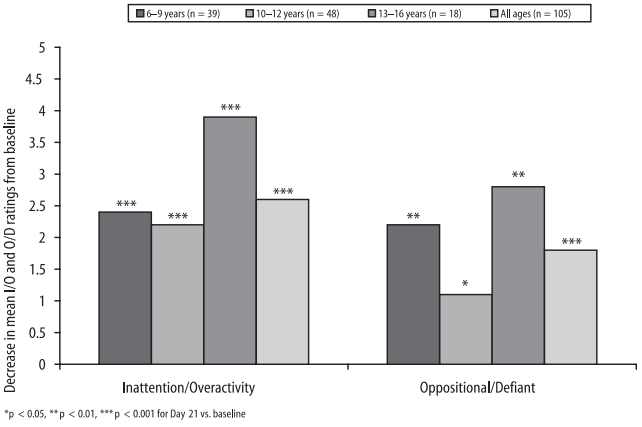

Fig. 1 Mean change from baseline in parent/caregiver IOWA Conners I/O and O/D ratings by age

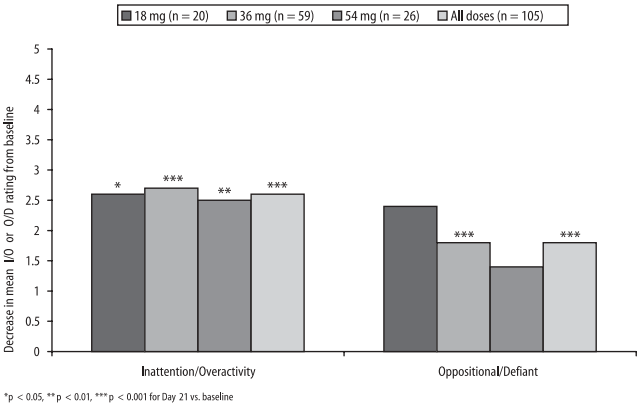

Fig. 2 Mean change from baseline in parent/caregiver IOWA Conners I/O and O/D ratings according to dose level

According to the GAE at Day 21, 74.3 % of parents/caregivers rated therapy as good or excellent for

their child. Parent/caregiver GAE rating increased with age (Fig. 3) and decreased with increasing dose level (Fig. 4). The GAE rating was higher for subjects with predominantly inattentive subtype compared with those with combined subtype (82.6 % vs. 71.4 %).

Similarly, investigators rated OROS® MPH therapy as good or excellent for 74.2 % of subjects, and GAE increased with age (Fig. 3). Investigator GAE ratings were similar across the three dose groups (Fig. 4), and were greater for the predominantly inattentive subtype (82.6 %) compared with the combined subtype (72.9 %). Teacher GAE ratings were lower than parent/caregiver or investigator ratings, but similarly showed an increase with increasing age (Fig. 3) and a higher rate for the inattentive subtype (57.9 %) compared with the combined subtype (51.7 %). Unlike parent/caregiver and investigator GAE values, the teacher rating for the 54 mg dose was almost double that for the two lower dose groups (Fig. 4).

Teacher IOWA Conners I/O and O/D ratings showed little change at Day 21 compared with baseline [change from baseline in IOWA Conners I/O, 0.4 ± 3.2 (p = 0.2552); change from baseline in IOWA Conners O/D, 0.2 ± 3.0 (p = 0.5310)]. A decrease in IOWA Conners I/O rating was observed in adolescents, but did not reach statistical significance [change from baseline in IOWA Conners I/O, –1.8 ± 3.9 (p = 0.1079); change from baseline in IOWA Conners O/D, –1.5 ± 3.1 (p = 0.0720)]. Effects according to dose and ADHD subtype were not consistent between IOWA Conners I/O and IOWA Conners O/D ratings.

At Day 21, 88.1 % of parents/caregivers said they would like their child to continue with OROS® MPH therapy. This rate was similar across age groups (83 %–100 %), dose groups (86 %–94.4 %) and for combined and predominantly inattentive ADHD subtypes (87.1 % and 91.3 %). A total of 84.8 % of subjects entered the follow-on study to receive OROS® MPH for up to 1 year.

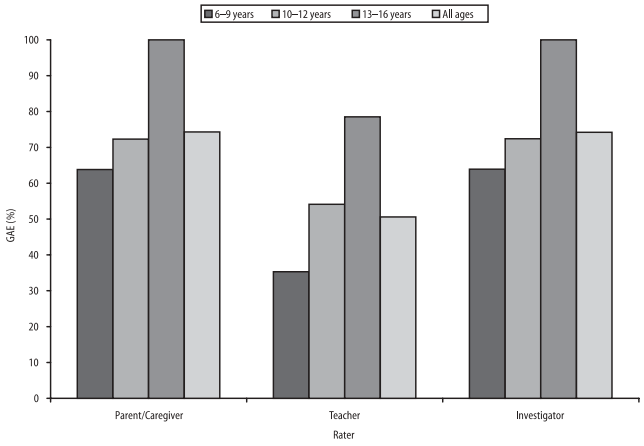

Fig. 3 Global Assessment of Effectiveness at Day 21 according to age group

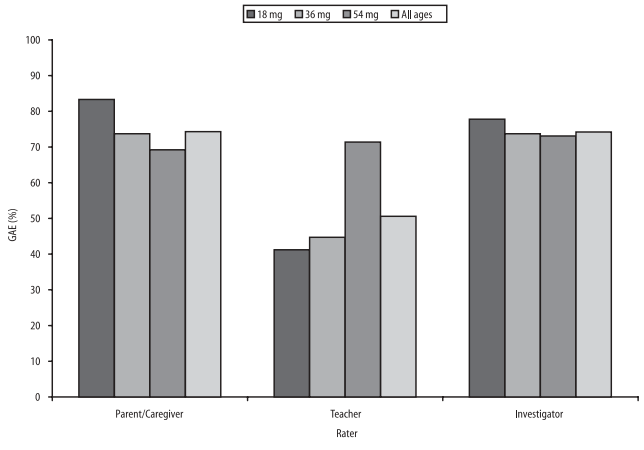

Fig. 4 Global Assessment of Effectiveness at Day 21 according to dose level

Adverse events

OROS® MPH therapy was well tolerated. A total of 55 subjects (52.4 %) reported 112 events in the course of treatment. Most events were mild or moderate in severity but 10 events reported by 7 subjects (6.7 % of study population) were considered severe. Of these, 5 were considered to be related to treatment [delayed sleep (1), headache (2), aggression (1), weight decrease (1)]. Seven subjects did not enter the follow-on study due to adverse events. Approximately half of the events (n = 64), reported by 42 subjects (40 %), were regarded as possibly, probably or definitely related to treatment. The only treatment-related adverse events reported in more than 2 % of subjects were: headache (11 events reported in 8 subjects; i. e. 7.6 %); abdominal pain (4 events in 4 subjects; i. e. 3.8 %); and tics (4 events in 4 subjects; i. e. 3.8 %). Treatment-related adverse events occurred slightly more frequently in the 36 mg dose group (30 subjects, 51 % of this dose group) than in the other two dose groups (18 mg: 7 subjects, 35 % of dose group; 54 mg: 5 subjects, 19 % of dose group).

Sleep quality was assessed as good or excellent by the majority of patients at baseline (56.2 %) and Day 21 (57.8 %) Whilst there were no important changes in sleep quality for subjects in the two higher dose groups, it was notable that sleep quality was assessed as good or excellent in 65 % of subjects at baseline and 84.2.% of subjects at Day 21 in the 18 mg group.

At baseline, 61.9 % of parents/caregivers rated their child's appetite as being good or excellent. During the course of the study, only 10.6 % (Day 7) or 9.8 % (Days 14 and 21) of parents/caregivers rated their child's appetite as being less than prior to study entry, while 22.1 % (Day 7) to 14.7 % (Day 21) rated their child's appetite as being greater than prior to study entry.

Fifteen subjects reported having a history of motor tics. At each assessment during the study, fewer than 9 subjects reported motor tics. No severe motor tics were experienced during the study. The number of subjects having verbal tics ranged from 1 at baseline to 3 at Day 21; none of the verbal tics were regarded as being severe.

Discussion

This is the first study to investigate the efficacy and tolerability implications of switching patients stabilised on IR MPH to OROS® MPH. It is also one of the few studies of OROS® MPH therapy performed outside the USA. Decreases in parent/caregiver IOWA Conners ratings over the course of the study suggest that switching was associated with an improvement in parent/caregiver-rated symptom control: both IOWA Conners I/O and O/D ratings decreased and the change from baseline was highly statistically significant. Teacher IOWA Conners I/O and O/D ratings suggest maintenance of symptom control in response to therapy switching.

The OROS® MPH dose for each subject was initially determined from their pre-study IR MPH dose using a recommended algorithm. Further adjustments in dose were allowed and were required by approximately 25 % of subjects. This suggests that switching from IR MPH to an appropriate OROS® MPH dose can readily be achieved, but with a need for further dose adjustment, in the short term.

The results of this study suggest that OROS® MPH is effective in controlling the symptoms of ADHD when it is treated in the European setting. OROS® MPH therapy was associated with an ADHD symptom level of approximately 5 according to parent/caregiver and teacher IOWA Conners I/O ratings. This represents an improvement in core ADHD symptoms over that typical of the unmedicated condition (e. g. a symptom level of approximately 10 [8, 15]). Similarly, IOWA Conners O/D ratings were approximately 5 (parent/caregiver) and 3 (teacher), compared with typical values of 9 for parent/caregiver ratings and 5 for teacher ratings of unmedicated subjects [8]. These ratings are similar to those previously reported for OROS® MPH therapy in children [8, 15]. At the end of the study, parents/caregivers and investigators reported therapy to be good or excellent for 74 % of subjects, while teachers rated therapy to be good or excellent for 51 %. These data are comparable with GAE ratings from a previous study of OROS® MPH in children that also reported lower ratings for teachers [18]. This may reflect differences between teachers and parents/caregivers in their expectations of children and differences in children's behaviour in the different environments.

Previous placebo-controlled, active-controlled studies [8, 15, 18] have demonstrated that the efficacy of OROS® MPH is comparable to that of IR MPH dosed three times daily in children. This appears to be confirmed in this study where switching from IR MPH to OROS® MPH was associated with a decrease in parent/caregiver IOWA Conners ratings and maintenance of teacher IOWA Conners ratings. All subjects in this study were stable on IR MPH doses of between 10 mg/day and 60 mg/day. The fact that only 7.6 % of subjects withdrew from entry to the follow-up study due to lack of efficacy suggests that most subjects whose symptoms are adequately controlled on IR MPH doses within this range can achieve at least as good symptom control with OROS® MPH doses of 18 mg/day to 54 mg/day. This study involved children and adolescents, supporting the efficacy of OROS® MPH across both age groups.

Some adolescents, however, may require a higher dose than 54 mg/day, as has been previously reported in a double-blind placebo-controlled study of OROS® MPH in adolescents (Wilens – manuscript in preparation). This study involved 177 adolescents with ADHD: 2 weeks of therapy with OROS® MPH was found to significantly reduce ADHD symptoms compared to placebo according to parent, investigator and patient ratings. In this adolescent study, subjects initially underwent dose titration to identify their individualised OROS® MPH dose. Four dosing levels were employed – 18, 36, 54 and 72 mg once daily. In all, 37 % of subjects required the maximum dose. This higher dose has now been approved for use in adolescents in the United States.

Therapy with OROS® MPH appeared to be well tolerated in this study. The adverse event profile corresponds to that previously reported for OROS® MPH in both short-term controlled studies and in two long-term open-label studies [16, 17, Stein, manuscript submitted]. As in previous studies, reported effects on sleep, appetite and tics were minimal.

Limitations

There are a number of limitations regarding this study that should be taken into account when interpreting the data.

This was an open-label, non-randomised, dose-adjustment study and the extent to which raters may have been biased by their knowledge of the medication cannot be assessed. The extent of placebo response can also not be assessed.

As the study design does not include a control group, the observed improvements in symptom control should be viewed with caution and may in part be due to the more rigorous physician and parent/caregiver attention that is possible in the clinical trial setting.

Subjects were receiving various IR MPH regimens at baseline, thus the impact of OROS® MPH on symptoms

compared to the unmedicated state was not assessed. In addition, subjects were all receiving MPH as their standard pre-study therapy; therefore, these data cannot necessarily be generalised to unselected children and adolescents in clinical practice who may not be responsive to MPH.

Differences between subgroups in symptom improvement may reflect how well symptoms were controlled on previous medication rather than in response to OROS® MPH.

The short duration of this phase of the study means that long-term effectiveness and safety issues are not addressed.

Conclusions

The results of this European study suggest that children and adolescents with ADHD will maintain and may achieve improved symptom control when switched from IR MPH to OROS® MPH. Improvement was more evident to parents/caregivers than to teachers, suggesting that the benefit may reflect improved symptom control in the period after school. This is consistent with the prolonged duration of action of OROS® MPH. The results of this study support the efficacy and tolerability of OROS® MPH, in children and adolescents, as demonstrated in previous studies.

In this study, most parents/caregivers wanted subjects to continue treatment with OROS® MPH. This may reflect the convenience of once-daily dosing – a significant advantage for patients and their parents/caregivers which is likely to promote better compliance.

Current international guidelines recommend the use of long-acting stimulant preparations over short-acting stimulants for the management of ADHD [5]. The results of this study provide further support for this recommendation and suggest that patients can readily be switched from IR MPH to OROS® MPH using an appropriate conversion algorithm. Longer-term follow-up of this study and accumulating clinical experience of OROS® MPH in ADHD should further clarify the benefits of effective once-daily therapy in the management of this disorder.

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