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Switching from immediate release to sustained release methylphenidate in the treatment of children and adolescents with attention deficit/hyperactivity disorder

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Abstract. – BACKGROUND: Switching from Immediate Release Methylphenidate (MPH-IR) to a sustained release formulation in treatment of attention deficit/hyperactivity disorder (ADHD) is often required to provide better compliance and convenience. However; the switch has been reported to be not always successful and small doses of MPH-IR may be added to sustained release preparations when its effect wears off.

SUBJECTS AND METHODS: In this survey, clinical case notes of 77 subjects aged 6-18 years who had been switched from MPH-IR to Concerta XL were retrospectively analyzed to demonstrate the effectiveness of the switch. The impact of adding MPH-IR to Concerta XL on the outcome was evaluated.

RESULTS: Switch to Concerta XL alone was successful in 94% of cases and all 23 (100%) subjects who had MPH-IR added to Concerta XL showed good response to the switch. However; more than 43% of the subjects required additional doses of MPH-IR and 55% needed a larger than recommended equivalent doses of Concerta XL for a successful switch.

CONCLUSIONS: Higher than equivalent doses of Concerta XL or an additional dose of MPH-IR may be required for a successful switch from immediate to sustained release methylphenidate.

Key words:
ADHD, Methylphenidate, Switch, Adolescents.

Introduction

Attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed neurobehavioural disorder in childhood, affecting over 5% of children worldwide[1] and 3-4% in the UK when DSM IV criteria applied[2].

In the UK, methylphenidate is the primary stimulant used in the treatment of ADHD despite limitations related to its time course of action. Its effect typically only lasts for four hours[3], which requires multiple daily dosing to control symptoms throughout day. On the other hand, longer acting stimulants offer greater convenience, confidentiality, and compliance with single daily dosing but may have greater problematic effects on evening appetite and sleep[4]. Concerta XL, an osmotic controlled-release formulation (OROS) has been reported to produce an extended duration of ADHD symptom control, consistent with an up to 12-hour duration of action[5,6] and to be both effective and safe for up to 2 years[7].

Switching patients from short acting to sustained release MPH-IR is sometimes required due to various reasons. Hoare et al[7] reported improved symptom control, compliance and parent/caregiver satisfaction with the switch, more commonly in patients in the older age group (10-16 years) and those on a higher dose (36 mg or 54 mg). Although these findings were supported in studies by Remschmidt et al[8] and Kordon et al[9], results from a retrospective study of usual clinical care conducted by Thompson et al[10] reported poor response to switch in a significant proportion (32%) of young people.

The present study was prompted by these conflicting results and the clinical experience of high success in switching psychostimulants in our specialist ADHD clinics at NHS Lothian. We hypothesized that particular variations in clinical practice might be responsible for this, particularly the use of top-up MPH-IR medication as an

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adjunct to once daily Concerta XL, and the use of higher than manufacturer's equivalent doses of Concerta XL when switching from MPH-IR.

Subjects and Methods

This is a retrospective survey of clinical case notes of all 75 children and adolescents aged 6-18 years who had a trial of sustained release methylphenidate (Concerta XL) in two specialist ADHD clinics in NHS Lothian between Jan 2004 and December 2010. The subjects were identified by computerised case load database and those with co-morbid psychiatric conditions (i.e. Oppositional Defiant Disorder, or Conduct Disorder) were included in the study.

Clinic letters were reviewed by the subjects' treating doctors to rate the ADHD symptom relief with MPH-IR alone, Concerta XL alone or Concerta XL with top-up MPH-IR. Prior to the data collection the clinicians met to define outcomes measures. Where available, teacher's "response to treatment reports", were included in the response evaluation. 'Poor response' was assigned to treatment if the patient's overall condition was documented to have deteriorated or the child developed significant side effects that led to termination of treatment. Parental reports of no change or improvement in child's behaviour or core symptoms of ADHD, positive teacher reports of improved behaviour, concentration or academic performance, better adherence to medication and the clinician's then positive impression were concluded as 'good response'. The reason for switching to Concerta XL was also recorded.

Statistical Analysis

A standardised data collection proforma was created on an excel spread sheet and the results were analysed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 16.0 for Windows. Data were mean ± SD. $p < 0.05$ was considered statiscally significant.

Results

A total of 74 young people participated in the study (64 males, 10 females), with a mean age 13 years 6 months (range 6 years 8 months-18 years 3 months, SD = 2.7 years).

The mean time since diagnosis was 4 years 1 month (range 5-141 months, SD = 30 months). The mean duration of treatment with MPH-IR was 1 year 5 months (range 2-494 weeks, SD = 92 weeks).

Response to MPH-IR Prior to Switch

Clinicians' rating of clinical response to immediate release MPH-IR was simplified into two categories of "good response" and "poor response" for analytical purposes. MPH-IR was rated as "not effective" for 11 subjects (15%) and 63 subjects (85%) showed some level of improvement, which was recorded as good response. The most common rating for MPH-IR before switching to Concerta XL was "minimally effective".

Response to Concerta XL Only

32 subjects were switched to an equivalent dose of Concerta XL, 17 to a lower dose and 24 to a higher dose (data for 1 case is missing). According to a two-tailed Chi Square test, the final dose of Concerta XL was significantly lower than the equivalent dose of MPH-IR for 16 subjects; significantly higher for 40 subjects and 16 participants were on the recommended equivalent dose. Therefore, after adjusting the dosage levels of Concerta XL, 16 people had switched from the manufacturer's recommended equivalent dose to a higher dose which was significant (x^2 (4) = 24.4, $p < 0.001$).

The mean Concerta XL dose at switch was 34 mg (range 18-63 mg, s.d = 13 mg) and the mean final dose was 42 mg (range 18-72 mg, s.d = 13 mg). There was a mean increase of 7 mg in Concerta XL dosage from the start dose to the final dose. A two-tailed Wilcoxon Signed Ranks Test found that this difference in dosage was significant ($z = -3.70$, $p < 0.001$). It was concluded that on switching from MPH-IR to an equivalent dose of Concerta XL, the dose of Concerta XL was not adequate and needed to be increased.

Response to Concerta XL alone and with top-up MPH-IR were initially grouped into five categories of "worse", "same", "minimally improved", "moderately improved" and "very improved" and then simplified into the categories; "good response" and "poor response" for analytical purpose. The most commonly rated response to the start dose of Concerta XL was "moderately improved" compared to their initial response to MPH-IR.

The data showed that the majority of participants had a good response to MPH-IR (Figure 1).

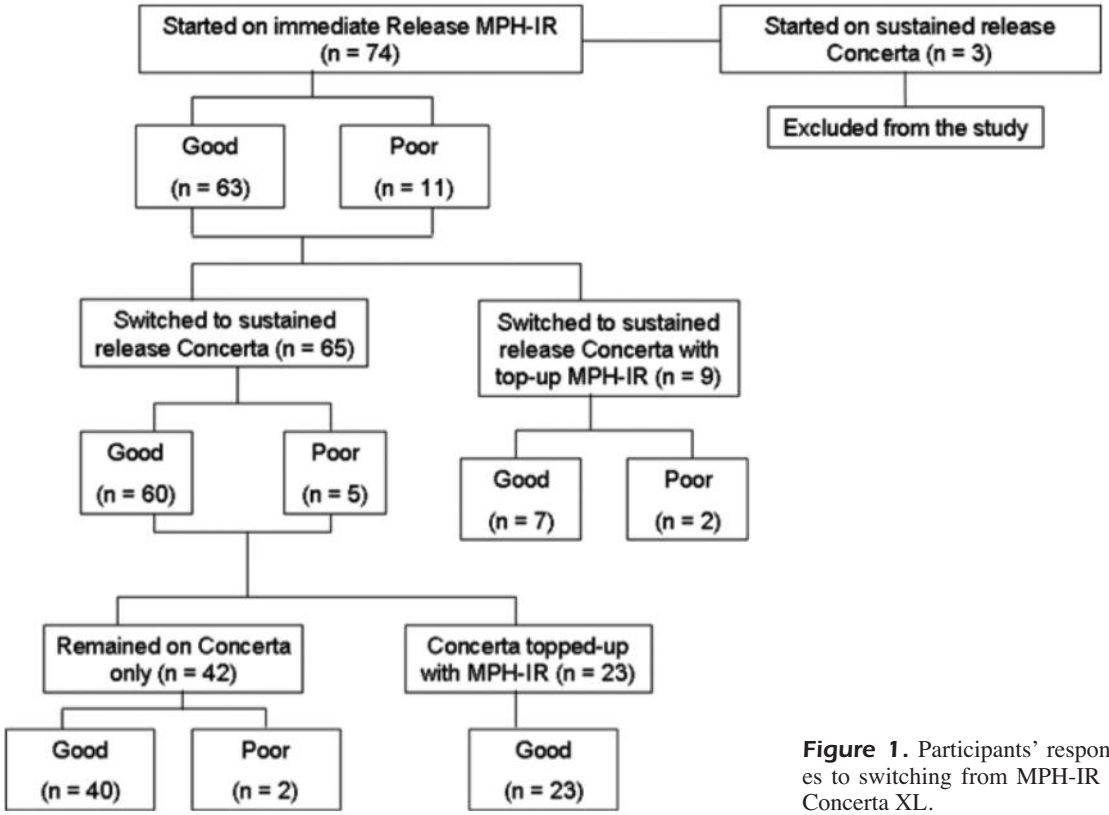

Figure 1. Participants' responses to switching from MPH-IR to Concerta XL.

Upon switching to Concerta XL (n = 65), there was a slight increase in the number of those who had "good response"; however, this difference was statistically not significant in McNemar's test; (x^2 (1) = 0.302 $p > 0.05$). McNemar tests were run on those participants who were switched to Concerta XL with top-up MPH-IR (n = 9) and this produced no significant changes in response (x^2 (1) = 1.00 $p > 0.05$). McNemar tests were also run on those participants who were initially switched from MPH-IR to Concerta XL and then later required top-up MPH-IR (n = 23) to see how their responses changed from taking MPH-IR. Results were not significant (x^2 (1) = 0.248 $p > 0.05$).

Response to Concerta XL with top-up MPH-IR

The mean top-up MPH-IR start and final doses were 10 mg (range 5-20 mg, SD = 4 mg) and 8 mg (range 0-30 mg, SD = 7 mg) respectively. This 2 mg drop from start to final dose was significant using the Wilcoxon Signed Ranks test ($z = -1.97$, $p < 0.05$). It was concluded that Concerta XL on its own was not adequate enough for 43% of the participants in this study (as 32 out of 74 participants required top-up MPH-IR alongside their dose of Concerta) and that a mean top-up dose of 8 mg of MPH-IR was needed. Clinicians reported some level of improvement in 88% of patients who received Concerta XL and top-up MPH-IR (Table I) and the most commonly rated response was "very improved".

4 out of 32 participants who required top-up MPH-IR received it in the morning only and 4 out of 32 had two doses of MPH-IR in the morning and afternoon. The remaining 24 participants (75%) only received afternoon dose of MPH-IR in addition to Concerta XL.

Mann-Whitney tests and Chi Square tests were conducted but failed to show any significant differences between poor and good responders in terms of the following possible confounding variables; gender, age, time since diagnosis, and dosage.

Convenience (45%) was the most common reason for switching from MPH-IR to Concerta XL. This included child and family preferences, embarrassment about taking tablets at school, school issues etc. The other common reasons were lack of efficacy (17%) and poor adherence (14%).

Discussion

We replicated the study conducted by Thompson et al[10] to measure successful switching from MPH-IR to Concerta XL in specialist ADHD clinics. The aim was to compare the outcome measures and speculate on the causative factors of any differences. In our study, additional dose of MPH-IR predicted a smooth switch to sustained release MPH without causing any additional adverse effects and the results confirmed our assumptions of a higher success rate when the care is provided in a Specialist ADHD Team setting. Two differences in clinical management of the transition were investigated. These were the use of higher than equivalent doses of Concerta XL when switched from MPH-IR and the use of additional dose of top-up MPH-IR. This survey demonstrated that Concerta XL on its own was not adequate for 43% of participants as 32/74 patients required top-up MPH-IR. Methodological constraints meant that although 87.5% of participants who received top-up MPH-IR with Concerta XL showed improvement in their condition, the difference was not statistically significant.

The mean MPH-IR dose at switch was 28.9 mg, which is equivalent to the 20% higher dose of Concerta XL (mean dose at switch 34 mg) required in the switch[3,11]. However, the final Concerta XL dose was 42 mg, which was significantly higher than its start dose. We concluded that larger than recommended equivalent doses of Concerta XL is needed for a successful switch.

All participants (23/23) who received top-up MPH-IR with their Concerta XL after staying on Concerta XL for a period of time (mean 21 months) showed improvement. We conclude that the positive effect of the top-up MPH-IR is clinically important for those who show limited symptom control on sustained release preparations. 54% (40/74) of the participants required a higher than manufacturer's recommended dose of Concerta XL for successful switching. These results suggest that clinicians may consider prescribing higher than equivalent doses of Concerta XL for an efficient transition.

This study also provides valuable information on the timeline of ADHD treatment in a natural setting (Figure 2). In 31% (23/74) of the participants MPH-IR was added to Concerta XL after a mean time of 1 year 8 months (Figure 2, Group 3). The top-up MPH-IR was well tolerated as it did not cause any increase in side effects. It is possible that other attributes of the specialist AHDH teams, i.e. close monitoring by multi-disciplinary staff and parent/teacher training programs also contributed to the highly successful transition rates.

This study suggests several criticims, some of which are those inherent to retrospective studies of small diverse clinical populations. The cross-sectional study is not the ideal design, the sample size is small and the data is restricted to two local centres only. Data collection and analysis were conducted by the same authors (inter-rater reliability not formally assessed) hence some degree of subjectivity is inevitable.

Future research in this area would benefit from a methodology that makes use of a more flexible and sensitive rating scales for measuring clinical outcome.

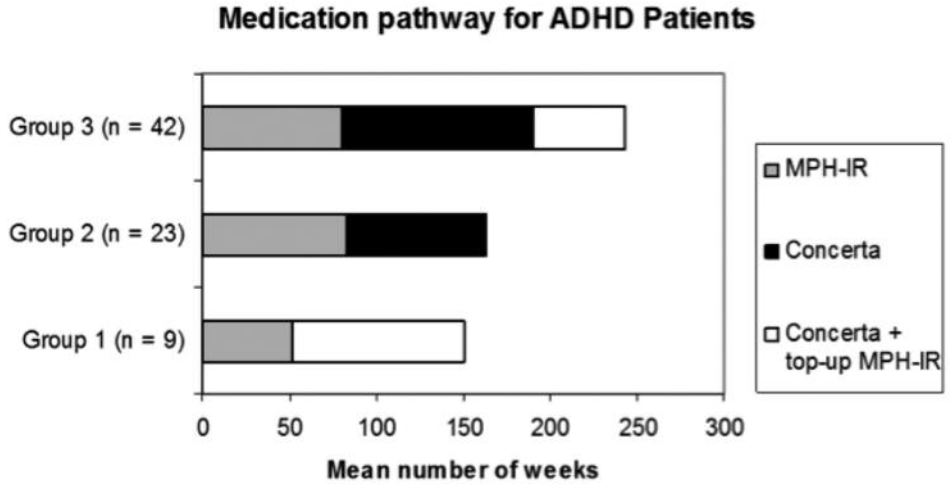

Figure 2. ADHD treatment pathway.

Conclusions

For a successful switch from MPH-IR, clinicians may need to consider using higher than recommended doses of Concerta XL or additional dose of MPH-IR to augment the effect of Concerta XL.

Additional dose of immediate release Methylphenidate may be successfully added Concerta XL without causing additional adverse effects.

Better results are likely if the care is provided in specialist ADHD clinics as compared to generic services.

Conflict of interest

The Authors declare that they have no conflict of interests.

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