

SHORT COMMUNICATION

SAFETY OF METHYLPHENIDATE FOLLOWING TRAUMATIC BRAIN INJURY: IMPACT ON VITAL SIGNS AND SIDE-EFFECTS DURING INPATIENT REHABILITATION

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Objective: The aim of the present study was to evaluate the safety of methylphenidate administered during inpatient rehabilitation following traumatic brain injury.

Methods: Forty inpatients with moderate-severe traumatic brain injury (mean 68.4 days post-injury) participated in a randomized, cross-over, double-blind, placebo-controlled trial of methylphenidate administered at a dose of 0.3 mg/kg body weight twice daily.

Results: Methylphenidate administration resulted in a statistically significant increase in pulse of 12.3 beats/min (95% confidence interval (CI) 9.25–15.36), diastolic blood pressure of 4.1 mmHg (95% CI 2.11–6.10), and mean arterial pressure of 3.75 mmHg (95% CI 1.79–5.72). These changes did not, however, appear to be symptomatic, as no participants were withdrawn due to adverse events, and there was no significant self-report of increased heart rate with methylphenidate. Blinding was successful. Significantly greater reporting of irritability of 0.14 points (95% CI 0.02–0.26), difficulty sleeping of 0.17 points (95% CI 0.02–0.31) and total side-effects of 0.68 points (95% CI 0.06–1.30) was associated with methylphenidate compared with placebo.

Conclusion: Methylphenidate given at 0.3 mg/kg body weight appears to be safe in the inpatient rehabilitation phase. This trial is registered with the Australian New Zealand Clinical Trials Registry (12607000503426).

Key words: methylphenidate, traumatic brain injury, rehabilitation, vital signs, side-effects.

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INTRODUCTION

The most commonly reported adverse effects associated with methylphenidate (MP) are anxiety, irritability, insomnia, headache and reduced appetite (1), along with increases in heart rate and blood pressure. Most studies investigating the safety of MP in those with chronic traumatic brain injury

(TBI) have found little evidence of significant side-effects (2, 3). In a well-controlled study, reduced appetite was the only significant adverse effect, and vital signs generally remained within normal limits (4). In the inpatient rehabilitation phase, the presence of side-effects has either not been documented (5, 6), or has been non-significant (7–9). With the exception of a retrospective chart review (8), there has been no systematic investigation of changes in vital signs. A recent randomized, double-blind placebo-controlled trial of 40 rehabilitation inpatients with TBI demonstrated a robust finding of faster speed of information processing with MP compared with placebo (10). The aim of the present study was to investigate the safety of using MP in the same TBI sample.

METHODS

Inclusion criteria were recent history of moderate-severe TBI as determined by the Glasgow Coma Scale (GCS) score and duration of post-traumatic amnesia (PTA) (11), and age between 16 and 60 years. Participants who reported a past history of significant psychiatric or neurological disease, treatment with MP, treatment for drug or alcohol dependence, seizure associated with the recent TBI, or current treatment with psychoactive medication were excluded. Forty participants with TBI were recruited from consecutive inpatient admissions (70% male), with mean age 26.4 years (range 18–49 years); mean time since injury 68.4 days (range 12–462 days); mean worst GCS 5.4 (range 3–13); and mean PTA duration 33.9 days (range 4–133 days). Weight-adjusted MP dosing resulted in the following distribution: 15 mg $n=11$; 20 mg $n=21$; 25 mg $n=7$; 30 mg $n=1$, all amounts taken twice daily.

Pulse, diastolic (DBP) and systolic (SBP) blood pressure, and mean arterial pressure (MAP) were recorded. The Side-Effects Questionnaire (SEQ) required participants to rate the frequency of 20 side-effects on a 4-point Likert scale. Adverse events spontaneously reported by participants were documented. Approval was obtained from relevant ethics committees, and participants provided informed consent. Over a period of 2 weeks participants were seen for 6 sessions (on Mondays, Wednesdays and Fridays), divided into 3 blocks as follows: days 1 and 2; days 3 and 4; days 5 and 6. One session of each block was assigned MP, the other placebo. This generated 8 possible administration sequences, and allocation was independently randomized. MP was administered at a dose of 0.3 mg/kg twice daily, rounded to the nearest 2.5 mg, at 08.00 h and 12.00 h, concealed in opaque gelatin capsules. Lactose in identical capsules served as placebo.

Assessment was undertaken 90–120 min after capsule administration. As safety data did not meet parametric assumptions, non-parametric

statistics were applied. Normal vital signs were classified according to the World Health Organization (WHO) definitions as follows: pulse < 100 bpm; SBP < 140 mmHg; DBP < 90 mmHg; and MAP < 107 mmHg.

RESULTS

Wilcoxon matched-pairs signed-ranks tests revealed a statistically significant increase in pulse of 12.3 beats/min (bpm) (95% CI 9.3–15.4), DBP of 4.1 mmHg (95% CI 2.1–6.1) and MAP of 3.8 mmHg (95% CI 1.8–5.7) associated with MP administration as compared with placebo (Table I). The largest individual increase in pulse with MP was 32.7 bpm, resulting in a pulse of 122 bpm, and the greatest increase in MAP was 16.4 mmHg, with a resultant MAP of 96.1 mmHg. Whilst there was little difference in the number of participants with abnormal SBP, DBP or MAP between the MP and placebo conditions, 11 participants (34.4%) with a normal pulse on placebo experienced an abnormal pulse/tachycardia whilst on MP. There was no statistically significant difference between those whose pulse did ($n=11$) and did not ($n=21$) become abnormal with MP on the basis of age (Mann-Whitney $U=92.5$, $p=0.360$), worst GCS (Mann-Whitney $U=69.5$, $p=0.401$), time since injury (Mann-Whitney $U=113.5$, $p=0.937$) or baseline pulse (Mann-Whitney $U=69.5$, $p=0.068$) or MAP (Mann-Whitney $U=91.5$, $p=0.487$). There were no significant correlations between weight-adjusted MP dose and increase in pulse, SBP, DBP or MAP (all $p>0.10$).

Although the overall ratings for all side-effects in both drug conditions fell in the mild range, Wilcoxon matched-pairs signed-ranks tests revealed significantly greater reporting of irritability of 0.14 points (95% CI 0.02–0.26), difficulty sleeping of 0.17 points (95% CI 0.02–0.31) and total side-effects of 0.68 points (95% CI 0.06–1.30) with MP compared with placebo. Despite the change in vital signs evident with MP, participants did not subjectively report significantly increased heart rate with MP compared with placebo. No participants were withdrawn from the trial due to adverse events. There were 3 reported instances of adverse events not captured by the SEQ: urinary tract infection; lower limb deep venous thrombosis; and profuse sweating.

No significant relationship between actual randomization (MP/placebo) and randomization guess for sessions 1, 2, 3, 5

Table I. Vital signs in patients administered methylphenidate (MP) or placebo

	MP	Placebo	p	Cohen's d
	Mean (SD) min/max	Mean (SD) min/max		
Pulse	102.3 (14.2) 73.3/136.7	89.9 (11.7) 71.0/117.0	<0.001	1.29
Systolic BP	121.8 (13.6) 100.7/165.3	119.2 (15.4) 92.5/171.3	0.08	0.30
Diastolic BP	77.4 (8.8) 56.0/98.3	73.3 (8.4) 53.0/95.3	<0.001	0.66
MAP	92.4 (9.0) 70.9/120.7	88.7 (9.6) 66.2/120.7	<0.001	0.61

BP: blood pressure; MAP: mean arterial pressure; SD: standard deviation.

or 6 was identified with separate Pearson's χ^2 tests for each session ($p>0.2$ for all).

DISCUSSION

This is the first randomized, placebo-controlled, cross-over study to examine the potential sympathomimetic effects of MP in the inpatient rehabilitation phase. The overall increase in MAP of 3.8 mmHg with MP was relatively small, as was the increase in DBP of 4.1 mmHg. There was no significant increase in SBP with MP. The average increase in pulse with MP compared with placebo of 12 bpm indicates a moderately significant increase. For 34% of those with a normal pulse on placebo, MP administration was associated with an abnormal pulse. We were unable to identify any differences between those whose pulse did and did not become abnormal with MP in terms of demographics, injury severity (worst GCS) or baseline vitals. There was no correlation between MP dose and increase in vital signs, suggesting that this weight-adjusted dosing was appropriate in this TBI population.

Demonstrated autonomic nervous system dysfunction in patients with TBI in the first few months post-injury (12) may lead to an increased vulnerability to the autonomic stimulation associated with MP in some patients. Whilst the present study findings suggest that the drug is generally safe in this population, an increase in pulse did occur in some participants. This risk was unrelated to age, injury severity, baseline vitals or concurrent medication.

TBI participants did not report a significant increase in heart rate with MP on the SEQ, suggesting that the increase in pulse did not result in a clinically detectable change to the participants. This was further supported by the success of blinding in the trial, indicating that participants were not able to differentiate drug condition on the basis of cardiac changes.

If statistical corrections for multiple comparisons had been applied, then the report of side-effects between drug and placebo conditions would not differ; however, the authors were interested to preserve power and identify any possible effects associated with MP administration. Participants with TBI reported mildly increased irritability and difficulty sleeping with MP compared with placebo. Longer acting MP preparations may alter the side-effect profile, and have the benefit of once daily administration.

MP was administered on only 3 occasions. Greater frequency or severity of side-effects with MP could be associated with more prolonged treatment. There was no incidence of seizures throughout the trial, with only 8 of the 40 participants concurrently treated with prophylactic anticonvulsants. This is consistent with previous reports that MP is not associated with increased seizure risk in TBI populations (13). Participants with a seizure history were, however, excluded, as were participants with a cardiac, psychiatric, drug or alcohol treatment history, potentially limiting generalization of the findings. Future studies could recruit from a more diverse TBI population in order to determine the safety of MP in the post-acute phase in those with a significant medical history.

In conclusion, this study has demonstrated the safety of MP for use in those in the early rehabilitation period following TBI. Monitoring of objectively measured vital signs may be warranted in samples with other risk factors that were excluded from the present study.

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