Effects of Long-Acting Methylphenidate on Heart Rate and Blood Pressure Among Patients with Acquired Brain Injury

David T. Burke, MD, MA
Sang Ryong Lee, MD
Richard Goldstein, PhD
Jessica Schutzbank, MD
Heechin Chae, MD

Harvard Medical School Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, Boston, Massachusetts

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ABSTRACT

Objective: The purpose of this study was to evaluate the effects of long-acting methylphenidate on heart rate and blood pressure among patients with acquired brain injury (ABI) undergoing treatment at an inpatient rehabilitation facility.

Design: The records of 60 consecutive hospitalized patients with ABI who had been treated with long-acting methylphenidate were reviewed. Twenty-four patients met the inclusion criteria. Systolic blood pressure, diastolic blood pressure, and heart rate recordings were compared before and after the introduction of long-acting methylphenidate.

Results: There was no significant difference in mean systolic blood pressure, diastolic blood pressure, and heart rate among patients before and after receiving long-acting methylphenidate.

Conclusion: This retrospective study supports previous research suggesting that clinically relevant doses of long-acting methylphenidate will not significantly affect the blood pressure or heart rate among patients with acquired brain injury.

INTRODUCTION

Methylphenidate (MP)[1] is widely used by physicians to treat patients with acquired brain injury (ABI). MP is known to increase the concentration of dopamine, an inhibitory neurotransmitter, at the synaptic cleft by blocking dopamine reuptake transporters[2] and releasing stored pools of endogenous dopamine.[3] MP is a short-acting psychostimulant that is categorized as an indirect agonist. It also seems to act by enhancing the activity of dopaminergic projections to the striatum, limbic cortex, and frontal cortex.[3] In addition, MP seems to influence monoaminergic neurotransmitters, thereby improving memory processing. Consequently MP is often a common drug for the treatment of ABI patients.[3]

In the past decade, several studies have supported the use of MP in

patients with ABI. Mooney and Haas demonstrated a significant reduction in anger and general psychopathology among patients with ABI who were taking MP.[4] In a double blind, placebo-controlled trial, Plenger and colleagues studied the effects of MP on attention, memory, and executive function in subjects shortly after ABI.[5] The authors concluded that MP improved the rate of recovery from ABI, but not long-term outcome. Whyte and colleagues examined the effects of MP on attention in patients with ABI who had been referred for outpatient care specifically for assessment and treatment of difficulties with attention.[6] They demonstrated that MP has a positive effect on processing speed, sustained attention, and phasic arousal. By virtue of its effect on speed of processing, it was concluded that MP might also improve consolidation of and retrieval of memories.[1] The results reported in a follow-up report Whyte and colleagues are among the strongest to date suggesting positive effects of MP on speed of processing in particular, and perhaps also on sustained attention and phasic arousal of outpatients with a diagnosis of traumatic brain injury (TBI).[7]

One area of concern with the use of MP is its potential effect on heart rate and blood pressure caused by the drug's sympathomimetic effects. Because MP is used most extensively in children with attention deficit hyperactivity disorder (ADHD),[8] most studies concerning the sympathetic nervous system effects of MP have investigated this population. In a blinded, placebo-controlled study, Ballard and colleagues measured the effect of MP on heart rate, blood pressure, and oxygen consumption in 27 hyperactive children during rest, exercise, and recovery.[9] Although oxygen consumption did not change, heart rate and blood pressure significantly increased in the methylphenidate group. There also was a significant correlation between dose per kilogram and the increase in heart rate and blood pressure. Other studies support these findings, particularly the effect of MP on blood pressure.[10-13] The documented variations in heart rate and blood pressure in children receiving MP have cautioned some physicians to monitor these patients' vital signs carefully and alter therapy accordingly.[9]

Because of the limited use of MP in adults, few studies exist that have examined its sympathetic nervous system effects in this population. Joyce and colleagues[14] showed that intravenous infusion of MP (0.3 mg/kg) in healthy subjects resulted in significant increases in plasma epinephrine, heart rate, and systolic and diastolic blood pressures. Volkow and colleagues[2] compared in vivo effects of MP on healthy patients and on known cocaine abusers and demonstrated that MP increases heart rate and blood pressure. Yet, there are few studies to date that examine the effects of orally administered, clinically relevant doses of MP in adults and, in particular, in patients with ABI. There have been but a few uncontrolled studies and case reports focusing on the effects of MP for patients with TBI.

In a previous retrospective clinical trial we found that patients on our brain injury unit did not have statistically significant changes in blood pressure or heart rate after the introduction of MP. As the blood pressure and heart rate were taken before breakfast and at lunch break, we did note that, as the vitals were taken outside of the peak blood levels, we might miss the peak effects of the drug. For this reason, we sought to review cases of individuals who were introduced to a long-acting MP (Concerta; ALZA corporation, at McNeil Consumer and Specialty Pharmaceuticals, a Division of McNeil-PPC, Inc, Fort Washington, PA) to allow

Table 1: Blood pressure and heart rate at baseline vs. peak dose for long-acting methylphenidate.

	Baseline (SD)	Peak (SD)	Coefficient	*P*-value
Systolic blood pressure*	116.6 (15.3)	111.2 (17.1)	5.41	0.225
Diastolic blood pressure *	68.4 (10.9)	67.6 (10.8)	0.84	0.756
Heart rate†	79.8 (14.3)	79.4 (12.7)	0.49	0.840

SD=standard deviation
*mmHg
†beats per minute

for a further assessment of the effects of MP. Because Concerta has a longer half life than methylphenidate, we felt that we could better capture the effect of this medication in a clinically relevant inpatient setting.

The goal of this study was to evaluate the effects of long-acting MP on adults with ABI with respect to sympathetic nervous system changes, specifically heart rate and blood pressure.

STUDY

Methods

This study reviewed the medical records of all patients who received long-acting MP during their hospital course at the ABI unit at Spaulding Rehabilitation Hospital. All patients were diagnosed with TBI, intracranial hemorrhage (ICH), or anoxic brain injury. Only those patients whose long-acting MP was introduced during the course of their inpatient stay were included in the chart review.

The records of 60 consecutive hospitalized patients with ABI were retrospectively reviewed for those who had been treated with long-acting MP. Twenty-four patients met the inclusion criteria of having been introduced to long-acting MP during their inpatient rehabilitation stay. All medications were given at 8:00 am. The modal dose was 36 mg. All blood pressure and heart rate readings were taken just before the morning medications (11:00 pm to 7:00 am shift), during the 12:00 pm to 1:00 pm lunch hour (for the 7:00 am to 3:00 pm shift), and at 8:00 pm to 9:00 pm (3:00 pm to 11:00 pm shift).

Comparisons were made separately for systolic blood pressure, diastolic blood pressure, and heart rate. Comparisons were made between similar shifts of baseline and peak medication periods as well as between the 11:00 pm to 7:00 am shift (premedication) and the 7:00 am to 3:00 pm shift (peak dosing period) during the medication period of the trial.

For patients who were initially prescribed short-acting MP and switched to long-acting MP, data were recorded for the baseline, as well as the peak dose for both the short-acting as well as the long-acting MP. Vital sign were not taken at calculated peak blood levels because patients were usually participating in therapy at those times. We felt that the patients' heightened metabolic status during exercise could obscure the effects of the MP.

Results

Our initial evaluation of the effect of long-acting MP compared the baseline values of blood pressure and heart rate with the readings obtained during the shift at the time when the patient was on the peak dose of long-acting MP (Table 1). For systolic blood pressure, the baseline mean was 116.3 mmHg while the peak dose mean was 111.2 mmHg. The trend was for a decrease in blood pressure, though this did not reach statistical

Table 2: Blood pressure and heart rate during 11:00 pm to 7:00 am shift vs. values during 7:00 am to 3:00 pm shift.

	11:00 pm–7:00 am (SD)	7:00 am–3:00 pm (SD)	Coefficient	*P*-value
Systolic blood pressure *	111.5 (21.9)	108.5 (16.7)	1.50	0.490
Diastolic blood pressure *	65.9 (11.9)	67.5 (11.3)	0.82	0.515
Heart rate†	74.8 (12.8)	78.4 (14.1)	1.82	0.200

SD=standard deviation
*mmHg
†beats per minute

significance (*P*=0.225). A similar comparison was made for diastolic blood pressure, with the baseline mean of 68.4 mmHg and the peak dose mean of 67.6 mmHg. This also failed to reach statistical significance (*P*=0.756). For heart rate, the mean baseline was 79.8 bpm and the mean peak dose heart rate was 79.4 bpm. The difference failed to reach statistical significance (*P*=0.840).

Looking at only the time period when the peak dose was being administered, we then compared the 11:00 pm to 7:00 am values with those collected during the 7:00 am and 3:00 pm shift (Table 2). We felt that this comparison would demonstrate the effect of the medication during that day, as the earlier shift would represent a time when little to no drug would be in the system, and the latter would reflect the time when the drug would be at near peak level. The mean systolic blood pressure for the 11:00 pm to 7:00 am shift was 111.5 mmHg and for the 7:00 am to 3:00 pm shift was 108.5 mmHg. This difference was not statistically significant (*P*=0.490). For the diastolic blood pressure, the mean from the 11:00 pm to 7:00 am shift was 65.9 mmHg and the mean 7:00 am to 3:00 pm shift was 67.5 mmHg (*P*=0.515). For heart rate, the mean for the 11:00 pm to 7:00 am shift was 74.8 mmHg and the mean for the 7:00 am to 3:00 pm shift was 78.4 mmHg. This failed to reach statistical significance (*P*=0.200).

Finally, reviewing those values from the baseline period and comparing them with the peak dose period, but only focusing on the 7:00 am to 3:00 pm shift, we made our final comparisons (Table 3). In this comparison, the baseline systolic blood pressure was 116.3 and the peak dose systolic presssure was 108.5 mmHg (*P*=0.058). The mean diastolic blood pressure at baseline was 69.0 mmHg and peak dose was 67.5 mmHg (*P*=0.601). Finally, the baseline heart rate was 82.3 bpm and the peak dose heart rate was 78.4 bpm (*P*=0.204). Performing a regression with robust errors, the difference between baseline and peak again failed to reach statistical significance for systolic blood pressure, diastolic blood pressure, and heart rate (*P*=0.135, *P*=0.282, *P*=0.729 respectively).

DISCUSSION

The rationale for using psychostimulants, such as MP, derives from several sources. MP has long been used to improve attention and behavioral control in children and adolescents who suffer from attention deficit disorder. Particularly in children who respond clinically to MP, the drug has been shown to enhance verbal learning,[15] the ability to stay on task,[16] and the speed at which stimuli are processed for decision making.[17] In adults, MP has been used effectively as a treatment for depression, apathy, and arousal deficits in neurologic conditions such as stroke, dementia, and

Table 3: Heart rate and blood pressure at baseline and peak dose during 7:00 am to 3:00 pm shift only.

	7:00 am–3:00 pm Baseline (SD)	7:00 am–3:00 pm Peak (SD)	Coefficient	*P*-value
Systolic blood pressure *	116.3 (15.6)	108.5 (16.7)	7.71	0.058
Diastolic blood pressure *	69.0 (10.5)	67.5 (11.3)	1.45	0.601
Heart rate†	82.3 (14.4)	78.4 (14.1)	3.89	0.204

SD=standard deviation
*mmHg
†beats per minute

brain injury.[18,19] Therefore, a substantial rationale exists for exploring the potential benefits of MP in cases of ABI-induced attentional impairment. As this drug is commonly used among the patients on our unit, the potential benefits and side effects are of clinical significance with every patient.

MP and other psychostimulants have been used to treat ADHD since at least 1938, when it was discovered that benzdrine led to increased interest and effort in school for affected children.[20] Compared with the amphetamines to which it is chemically related, MP may affect mental functions more significantly than motor activity.[21.]

In a previous study, Burke and colleagues reviewed the effects of short-acting methylphenidate, using these same parameters, finding that there was no significant rise in any of the above parameters.[29] We did note, however, that there was a trend toward increased values with the use of short-acting MP. Because that study had not measured those values during the peak blood level, there may have been an effect that had not been measured at the time of the blood pressure and heart rate measurements, which were done as part of clinical care, and not timed to capture the maximum effect of the medication.

Alban and colleagues attempted to capture the peak blood level effect of short-acting methylphenidate among a series outpatients in a Brain Injury clinic.[30] Using a double blind, placebo-controlled, crossover methodology, MP was given at a dose of 0.3 mg/kg, twice per day. In this study, there was no significant change in blood pressure. There was however an average increase in heart rate of 7 bpm. The difference between the Burke and the Alban studies may reflect a peak blood level phenomenon, which is transient, and only evident during this peak period. For most patients this short-term rise may be of little clinical importance. As patients move from an inpatient to an outpatient setting, there is good reason to simplify their medication dosing. For this reason, once-per-day, long-acting MP is often used on our brain injury unit. We did not attempt to review the difference in effects of the 2 forms of MP, as this would be best done during the peak blood level periods. This may prove to be an interesting follow up to the current study.

It is worth noting that arbitrary peak values were established that we thought might, if breached, cause the therapists to consider reducing or stopping therapy. We recorded the number of times during the baseline and then in the treatment period where such values were reached or exceeded. We did not see any such violations in either the baseline or the treatment period. This seems to add some clinically useful data concerning the clinical significance of long-acting MP's effect on blood pressure and heart rate.

The difference between this paper

Table 4: Patients Demographics

Gender	Age	Diagnosis
F	39	TBI
F	77	TBI with ICH and hydrocephalus
F	43	TBI
F	60	Meningoma with CVA
M	77	CVA
F	48	Demyelinating encephalopathy
M	25	Anoxic brain injury subsequent to benign tumor removal
M	32	TBI
M	41	TBI, subdural hematoma
M	91	Anoxic brain injury
F	93	TBI
F	70	Anoxic brain injury
F	32	TBI
M	18	TBI, Right frontal parenchymal bleed, right temporal contusion
F	27	ICH, s/p AVM
M	48	Anoxic brain injury
M	20	TBI
M	40	TBI
M	53	TBI
M	22	TBI

TBI=traumatic brain injury
ICH=intracranial hemorrhage
CVA=cerebrovascular accident
AVM=arteriovenous malformation

and the Alban paper may not only be a result of a difference in medication use, but also in the context in which the parameters were measured. As the peak blood level for MP occurs during a period in which most of the brain injury patients are involved in therapies, it was our concern that making these measurements during that period might reflect an increase in metabolic rate as a result of recent therapies. We thought it more appropriate to measure blood pressure during a rest period (the 12:00 pm to 1:00 pm lunch period), which would better reflect the effect of the medication rather than the effect on a difference in activity level between 11:00 pm and 7:00 pm and 7:00 am and 3:00 pm.

What may be of further interest, however, is to determine the cardiovascular difference between periods during which the patient is taking either short- or long-acting MP and their response to similarly stressful physical activity. What was not tested in our study is whether patients' activity was reduced as a result of a response to activity that was exaggerated by the introduction of long-acting MP. If this were the case, then the therapists might be modifying the treatment sessions to accommodate for a cardiovascular response that was not measured well in this study. To test this effect one would have to, during the peak blood level period, use a predetermined effort level to compare the baseline, the MP, and the Concerta. This is certainly worthy of consideration for a future study.

Other studies of inpatients with

other clinical diagnoses have appeared in the literature. In a study by Lingam of 25 stroke patients, none showed a significant increase in blood pressure, even though 16 of the subjects had a previous diagnosis of hypertension.[26]

Similarly, Spencer and colleagues reported no significant changes in blood pressure when comparing MP with placebo in a randomized, double-blind, crossover study of adults with ADHD.[31] Although they did find an increase in heart rate and a decrease in weight with MP, the changes were not felt to be clinically significant, and a change in medication dose was not made.

Other population groups have been explored. For example, Jansen and colleagues treated depression and apathy among patients with cancer, cardiac disease, HIV, and strokes, as well as in the elderly.[34] There was no significant change in heart rate and blood pressure among these patients. This study also demonstrated no side effects. Rosenberg, in an uncontrolled study, reported on the efficacy of MP in 29 medically ill and depressed patients.[35] Three patients demonstrated tachycardia and hypertension and 4 complained of irritability and/or agitation. These side effects were reduced or eliminated with the reduction of the MP dose.

As newer long-acting MP has been introduced, some researchers have explored the possibility that this sustained release may change the hemodynamic profile compared with dosing with short-acting MP. Concerta peak blood levels occur at about 6 to 8 hours after oral administration. Its half-life is approximately 3.5 hours and its therapeutic effects last 12 hours.[32] Timothy and colleagues, over a 12-month period, reported that Concerta (osmotic-release MA) produced minor clinical, though statistically significant, changes in blood pressure and heart rate in children with ADHD.[33]

CONCLUSION

This study was proposed as a means to measure the effects of a longer-acting MP (Concerta) to determine whether those differences might be captured with values measured during the peak blood period. As the results demonstrate, this was not the case. This is comforting for those who use MP or the treatment of those with ABI. It is possible that there is a difference in the cardiovascular response of short-acting and long-acting MP, and that the product in short-acting MP may in fact still be found to have a cardiovascular effect that was not captured by either our preliminary study or this current study. To investigate this, we would have to time a mid-day blood pressure and heart rate measurement to coincide with the blood levels. On a rehabilitation unit this might be difficult because of activities that occur that may cause levels to rise as a result of exertion, and therefore might implicate the MP incorrectly. We would need to monitor a period of rest before such measurements and would therefore need to control the environment well to accomplish this. This type of perspective and disruptive study might prove useful and worthy of later consideration.

One of the weaknesses of this study was the lack of standardization of the dosing. As the dosing of the long-acting MP was determined by clinical response, there was no standardized dose described for research purposes. The modal dose was 36 mg/day. Several of the patients did receive 18 mg/day as the dose at which the clinical staff felt there was an adequate response for the treatment of their brain injury. As this may present with heterogeneous results based on different mg/kg dose distributions, we thought that this method might best reflect clinical practice. Also, it may be true that there is a step up effect, where doses below a certain level would

not negatively affect heart rate or blood pressure, while doses above this level may show such an effect. One may suspect this with the higher doses in the Alban study as well as the results of previous studies, which have alluded to a positive effect of MP among different patient populations dosed differently than the current study.

In conclusion, this study suggests that there is no statistically significant and certainly no clinically meaningful increase in blood pressure or heart rate among patients with ABI who were introduced to therapeutic doses of long-acting MP during their inpatient rehabilitation. MP peak blood levels occur at about 1 to 2 hours after oral administration. Its half-life ranges from 1 to 3 hours, and its therapeutic effects last 4 to 6 hours.[25] The effect of MP on vital signs has not been widely explored.

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