Methylphenidate in the Treatment of Coma

Michael Worzniak, MD; Michael D. Fetters, MD, MPH; and Maureen Comfort, MPH
Dearborn and Ann Arbor, Michigan

While there is significant morbidity and mortality involving patients in semicomatose and comatose states, the care of such patients has traditionally been limited to supportive measures. We report two cases of patients treated with methylphenidate hydrochloride: the first, a patient in a semicomatose state resulting from traumatic brain injury, and the second, a patient in a comatose state secondary to a subdural hematoma that occurred after a fall.

Treatment with methylphenidate may provide neurostimulations by augmenting the activity of injured neuronal tissue within the reticular activating system, and by amplifying the net effect of the reduced number of viable neurons.

Methylphenidate is a low-cost, potentially efficacious intervention for reducing the duration of comas, for preventing life-threatening and costly complications of prolonged unconsciousness, and for promoting early ambulation and recovery. Further research using more rigorous research designs to ascertain the effectiveness of methylphenidate in the treatment of patients in semicomatose and comatose states is needed.

KEY WORDS. Methylphenidate; coma; brain injuries; Glascow Coma Scale. *(J Fam Pract 1997; 44:495-498)*

Two case series[1,2] and case reports[3,4] suggest a role for methylphenidate in the reversal of coma resulting from various causes. Recent research suggests that methylphenidate can improve attention and functional outcomes during rehabilitation of acutely brain-injured adults,[5] and a recent review[6] suggests that psychostimulants are potential treatment options for neuropsychiatric sequelae of stroke and traumatic brain injury including depressive disorders, impulsiveness, apathy, irritability, attention, concentration, and memory problems. Despite these initial intriguing results, little follow-up investigation of the drug's utility, safety, and efficacy in the treatment of comatose and semicomatose states has been conducted.

In the following case reports, two patients were treated successfully with methylphenidate. In the first case, a patient was in a semicomatose state due to traumatic brain injury, and in the second, a patient was in a comatose state secondary to the subdural hematoma after a fall.

The patients' degree of coma was evaluated using the Glasgow Coma Scale (GCS). The scale has been used widely to classify the severity of decreased levels of consciousness using ocular, verbal, and motor responses to stimulation. The GCS provides an effective, simple, and reproducible method of assessing the degree of coma (Table). A patient with a score of 15 is considered normal, a score between 9 and 14 denotes a decreased level of consciousness or semicoma, and a score of 8 or less corresponds to coma.[7]

Submitted, revised, February 10, 1997.
From the Family Practice Residency, Oakwood Hospital and Medical Center (M.W.), Dearborn, and the Department of Family Practice, University of Michigan Medical Center (M.F. and M.C.), Ann Arbor, Michigan. Requests for reprints should be addressed to Michael Worzniak, MD, Family Practice Residency Program, Oakwood Hospital and Medical Center, 18101 Oakwood Blvd, PO Box 2500, Dearborn, MI 48123-2500.

Case Reports

Case 1

A 19-year-old man sustained cerebral lacerations and contusions resulting in severe cerebral edema and a small subdural hematoma after a motor vehicle accident. Initial interventions included ventilatory support and care at a major trauma center. Despite aggressive supportive treatment, he remained in a semicomatose state, and was transferred to a community hospital for nursing home placement. When transferred to a community hospital, he had decreased mental awareness, and responded minimally to pain. With deep stimulation his eyes fluttered and he yawned before slipping back into a semicomatose state. His pupils reacted sluggishly to light, and he responded to loud verbal commands by moving his left hand, which had a very weak grip. The baseline GCS score was 8.

Four days after admission, with the family's consent, treatment with methylphenidate 10 mg twice a day through a gastrostomy tube was initiated.

TABLE

The Glasgow Coma Scale

Test	Response	Score*
Eye opening	Spontaneous	4
	To speech	3
	To pain	2
	None	1
Best verbal response	Oriented	5
	Confused	4
	Inappropriate	3
	Incomprehensible	2
	None	1
Best motor response (arm)	Obedience to commands	6
	Localization of pain	5
	Withdrawal response to pain	4
	Flexion response to pain	3
	Extension response to pain	2
	None	1

*Scores are summed across the 3 categories. A score of 15 is normal, 9 to 14 indicates semicoma, and a score of 8 or less indicates coma. Data for table adapted from Teasdale G, Murray G, Porker L, et al. Adding up the Glasgow Coma Score. Acta Neuochirurgica Supplementum (Wien) 1979; 28:13.

Twenty-four hours later, there was a dramatic improvement in his level of consciousness. He appeared more alert, his pupils were more active, he touched his face with his hand, and he exhibited other spontaneous movements. The GCS score was 10. On day 3 of treatment, the dosage was increased to 20 mg twice a day, and on day 5, he responded to voice commands by holding his head up and making eye contact. When his parents brought in his class yearbook, he turned the pages with his left hand, although it was unclear whether he could identify anyone. Seven days after initiation of treatment, he began showing emotions such as anger and crying. His GCS score was 14.

On day 9, he began to feed himself, and asked to be discharged. He briefly stood on his own and transferred into a chair. On day 10, he conversed with a girlfriend, and while talking with his mother, he recalled the accident and cried as he expressed sorrow that it had happened. The dosing interval was increased to three times a day on the 14th day of treatment. After 18 days of treatment, he was verbal, ambulatory, and following commands. The GCS score was 15. He was discharged to a head injury facility for more intensive speech and physical therapy.

Case 2

An 89-year-old woman was admitted to a community hospital unresponsive and comatose. Her past medical history included hypertension, atherosclerosis, and cerebral thrombosis 1 year earlier that resulted in minimal residual deficit. A verbal woman at baseline, she had previously lived in a supervised adult care home, where she read and interacted with other patients and family. One week before admission she fell, and appeared to have sustained only minor injury. In the 24 hours before hospital admission, however, she appeared confused, and upon taking a nap, she became unresponsive.

At initial examination at the hospital, she appeared deeply comatose. She did not respond to pain, temperature testing, or touch. Her pupils were minimally reactive to light, and the right pupil was larger than the left. Her baseline GCS score was 3. A computed tomography scan of the head revealed a large subdural hematoma with herniation of the right cerebral hemisphere across the midline into the left cranium. As neurosurgical consultation estimated surgical mortality at near 100%, supportive care with intravenous fluids and nasal gastric feeding was elected. The patient was stabilized and transferred to a long-term care home 1 week after admission. She remained totally unresponsive, requiring nursing care, tube feeding, and frequent turning, suctioning, and bowel and bladder care.

After 1 month of unchanged status at the long-term care home, the family consented to treatment with methylphenidate. Six days after initiation of methylphenidate at 5 mg twice a day, she exhibited spontaneous eye movement and spoke one or two words. A GCS score of 10 was recorded. On day 15 of treatment, she could hold her head up and speak in short phrases. A GCS score of 14 was recorded. On day 27 of treatment, the dosage was increased to 10 mg twice a day and she began to remain awake most of the time. She

became more alert and in contact with her surroundings, and continued to use short phrases to communicate with the staff.

Further improvement occurred after the dosage of methylphenidate was increased to 10 mg three times a day. The nasal gastric tube was removed, and she was fed orally. Four days later she was alert and talkative and had a good appetite. She could sit in a chair and converse with the staff with appropriate speech and comprehension. Her GCS score was 15. She continued to do well until almost a year later, when she died of an acute cardiac event.

Discussion

This report describes the dramatic improvement of a patient in a semicomatose state from traumatic brain injury and of a patient in a comatose state from subdural hematoma after treatment with methylphenidate. Both patients progressed from a state of total dependency to the capacity for independent nutrition, ambulation, and communication.

Administration of exogenous methylphenidate to patients in comatose and semicomatose states may exert an influence by stimulating the reticular activating system. The bulboreticular facilitory area lies in the reticular substance of the middle and lateral pons and mesencephalon of the brain, and influences consciousness and awareness by regulating the excitability of the cerebral cortex.[8] Any insult to these nuclei reduces cortical stimulations and thereby leads to a reduction in consciousness. Methylphenidate stimulates the ascending reticular activating system, among other brain regions, by inducing the release and inhibiting the reuptake of catecholamines (particularly dopamine) in presynaptic neurons.[9] The psychostimulant properties of methylphenidate have been linked to its binding to a site on the dopamine transporter, resulting in inhibition of dopamine reuptake and enhanced levels of synaptic dopamine.[10]

While documentation of the precise mechanism is lacking, recent research illustrates lower mean cerebral uptake of an amphetamine isotope among craniofacial trauma patients with loss of consciousness compared with craniofacial trauma patients without loss of consciousness.[11] Kraus[6] postulates that depletion of monoaminergic transmission may underlie the neurobehavior disorders in traumatic brain injury and poststroke disorders. By analogy, there may be even more profound deficiencies of monoamine-like substances in patient with loss of consciousness. Hence, methylphenidate may provide neurostimulation by augmenting the activity of injured tissue within the ascending reticular activating system, and by amplifying the net effect of the reduced number of viable neurons.

There are no clear guidelines established for daily dosage of methylphenidate in brain-injured patients; therefore, gradual titration of dosage with close monitoring for side effects is advised. In patients with brain injury due to stroke or trauma, methylphenidate can be started at 5 mg twice a day. The dose can be increased by 5 to 10 mg every 2 days, using divided doses, with monitoring of vital signs and assessment for adverse effects.[6] The adult maximum daily dose range is 60 to 80 mg.[9] Methylphenidate has been utilized as a first-line pharmacological agent because of its rapid onset of action and acceptable side-effect profile.[5] Potential objective side effects include blood pressure changes in either direction, dysrhythmia, and tremor. Twenty geriatric patients with chronic medical illness were treated with methylphenidate. Seven patients in this group had cardiac disease (two with aortic insufficiency; one with atrial fibrillation; four with congestive heart failure). None of these patients encountered problems such as palpitations, blood pressure fluctuation, arrhythmia, or worsening failure when treated with methylphenidate.[12]

Conclusions

A low-cost intervention to reduce the duration of coma, to prevent life-threatening and costly complications of unconsciousness, and to promote early ambulation and recovery is needed. Methylphenidate shows promise for shortened hospitalizations, reduced complications, and improved outcomes for patients in comatose and semicomatose states. Further research using more rigorous research designs to ascertain the effectiveness of methylphenidate in the treatment of patients in semicomatose and comatose states is needed.

ACKNOWLEDGMENT

Debbi White provided invaluable assistance in manuscript preparation.

REFERENCES

1. Hoagland RJ. Pharmacologic treatment of coma of diverse origin. Am J Med Sci 1965; 249:623-35.
2. Boet J, Ordaz P, Matute M, De Ponce C, Ponce Ducharne PL. Uso Del metil-phenidate (Ritalin) en comas de Diverso origen. Arch Hosp Vargas 1971; 13(1&2):103-14.
3. Schleissner LA. Glutethimid intoxication with prolonged coma and hyperpyrexia treated with methylphenidate. Calif Med 1966; 105:41-4.
4. Lichtigfeld FJ, Gillman MA. Methylphenidate for reversal of drug-induced coma. Clin Neuropharmacol. 1990; 13:459-60.
5. Kaelin DL, Cifu DX, Matthies B. Methylphenidate effect on attention deficit in the acutely brain-injured adult. Arch Phys Med Rehab 1996; 77:6-9.
6. Kraus MF. Neuropsychiatric sequelae of stroke and traumatic brain injury: the role of psychostimulants. Int J Psychiatry Med 1995; 25:39-51.
7. Jenett B. Assessment of the severity of head injury. J Neurol Neurosurg Psychiatry 1976; 39:647-55.
8. Guyton AC. Textbook of medical physiology. 8th ed. Philadelphia, Pa: WB Saunders Co, 1991: 648-9.
9. Kaplan HI, Sodock BJ. Psychiatric drug treatment. Baltimore, Md: Williams & Wilkins, 1993:168.
10. Ding YS, Fowler JS, Volkow ND, et al. Pharmacokinetics and in vivo specificity of [^{11}C] dl-threo-methylphenidate for the presynaptic dopaminergic neuron. Synapse 1994; 18:152-60.
11. Ducours JL, Role C, Guillet J, San Galli F, Caix P, Wynchank S. Craniofacial trauma and cerebral SPECT studies using N-isopropyl-iodo-amphetamine (1 2 3 I). Nucl Med Commun 1990; 11:361-7.
12. Satel SL, Nelson JC. Stimulants in the treatment of depression: a critical overview. J Clin Psychiatry 1989; 50:241-9.