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Annals of Pediatrics & Child Health

Case Report

Amantadine Use in an Infant with Abusive Head Trauma: A Case Report

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Submitted: 08 May 2020

Accepted: 21 May 2020

Published: 25 May 2020

ISSN: 2373-9312

Keywords

- Abusive head trauma; Traumatic brain injury; Infant; Amantadine; Recovery

Abstract

Accidents and trauma, including abusive head trauma (AHT), are leading causes of death and disability in children. One of the most common sequelae of AHT in children is traumatic brain injury (TBI), of varying severity. Amantadine, a dopamine agonist, is one of the most commonly prescribed medications for prolonged disorders of consciousness (DOC) after TBI and has been proven to facilitate a faster rate of recovery. The purpose of this case study was to examine the effectiveness of amantadine on alertness and cognitive and physical function in a ten-month-old female infant with chronic AHT six months post-injury. The infant girl in this case had shown minimal recovery in the 6 months following injury until the time when she was started on amantadine. She remained on amantadine for a total of 19 months and the medication was well tolerated. Her development was closely monitored and she demonstrated significant improvements in her motors skills, socialization and speech during this period. This case supports the use of amantadine in infants, even in cases of chronic brain injury and prolonged DOC, to bring meaningful change to cognitive and motor function. It is still unclear at what point amantadine can be safely discontinued without regression of skills, but in this case, the patient took amantadine for over one year and was safely weaned off medication without signs of regression. Further studies are needed to provide additional evidence on the efficacy of amantadine in children with TBI, including in younger ages.

ABBREVIATIONS

AHT: abusive head trauma; TBI: traumatic brain injury; DOC: disorders of consciousness; PM&R: physical medicine and rehabilitation; MAS: Modified shworth Scale

INTRODUCTION

Accidents and trauma are leading causes of death and disability in children from infancy through adolescence. Traumatic brain injury (TBI) related visits to the emergency room were highest for children from zero to four years of age and primarily associated with assault and motor vehicle traffic-related crashes [1]. The CDC estimates that 1 out of 7 children are victims or child abuse and neglect, including abusive head trauma [2].

Abusive head trauma (AHT), previously identified as shaken baby syndrome or non- accidental head injury, is broadly defined as injury of the skull and intracranial contents as a result of perpetrator-inflicted force. Abusive head trauma is most common in children between 3 to 8 months of age and is the primary cause of death and disability in infants and young children [3]. AHT represents a persistent and significant disease burden in children under the age of 4 years and child abuse is known to be a major cause of brain injuries in children [3,4]. When compared to age-matched controls in typical single occurrence accidental TBI, mortality after AHT is disproportionately high and likely attributable to key differences between injury phenotypes [4]. AHT is frequently excluded from studies of childhood TBI, therefore there is very limited knowledge regarding the treatment for significant brain injury in this group during and after acute medical care.

One of the greatest challenges in managing brain injury recovery is treating disorders of consciousness (DOC), including impaired arousal and attention. Prolonged DOC has been shown to be a poor prognostic factor for recovery after TBI. Amantadine hydrochloride, a dopamine agonist [5], is one of the most commonly prescribed medications for prolonged DOC after TBI and has been proven to facilitate a faster rate of cognitive recovery with improvement in alertness, arousal and consciousness in people with severe TBI [6].

Amantadine was initially used as an antiviral drug but is now more commonly used for its dopaminergic properties to treat conditions such as Parkinsonism and other movement disorders. Amantadine operates both presynaptically and postsynaptically to facilitate dopamine release and delay dopamine reuptake, allowing for increase in the binding efficiency through an increase in receptors [7]. Amantadine has been used off label for the treatment of TBI since the 1980's and has been shown to improve arousal levels after TBI, regardless of type, severity

and duration of injuries or patients' age [8-10]. Amantadine also accelerates the pace of functional recovery during active treatment in patients with post-traumatic DOC [6]. By achieving earlier improvement in arousal and awareness with amantadine, these patients are able to participate in rehab sooner to facilitate the recovery process [11]. After the medication has been weaned, a slower rate of recovery has been observed; however gains are typically maintained without a regression in skills [6,11]. While there is a large body of evidence supporting the use of this medication in the treatment of TBI, including DOC, there is limited research of its use in the pediatric population.

Existing pediatric research studies are mostly focused on children over the age of six years in which treatment with amantadine began in the acute stage post-injury [7,9,12,13]. The purpose of this case study was to examine the effectiveness of amantadine on physical function and alertness in a ten month old female infant with a chronic abusive head trauma and low arousal level, consistent with prolonged DOC, when treatment with amantadine was initiated six months post-injury.

CASE PRESENTATION

This ten month old infant girl, who was born full term without complications, presented to our outpatient pediatric physical medicine & rehabilitation (PM&R) clinic with diagnosis of right hemiparesis secondary to abusive head trauma, injuries consistent with shaken baby syndrome, that occurred at age 3.5 months. At time of injury, she was brought to the emergency department in status epilepticus and required urgent intubation for airway protection. Initial brain MRI showed subdural hemorrhagic product overlying left cerebral hemisphere, parenchymal hemorrhage in left parietal lobe, & subtle ischemia. Other imaging found additional bony fractures in various stages of healing and bilateral retinal hemorrhages. She was intubated and sedated for 9 days while seizures were being managed and she spent a total of 2 weeks in the pediatric intensive care unit followed by admission to inpatient rehabilitation facility for intensive therapies. She was discharged on levetiracetam for seizure management and remains on levetiracetam due to continuous abnormal EEGs (Table 1).

Her initial presentation in our outpatient pediatric PM&R clinic was 6.5 months after injury when she was ten months old. Referral reasons included concern regarding generalized developmental delay and for evaluation for possible botulinum toxin injections for spasticity management. At time of initial evaluation, patient presented with diagnosis of right hemiplegia and demonstrated no active movements of her right arm or right. On examination, she had mild spasticity in all four extremities (Modified Ashworth Scale (MAS) 1+) with right side more involved than left. She was unable to sit independently when placed, complete rolling due to inability to clear arm, bring chest off surface in prone, and had minimal interest in toys. She was minimally responsive to social interactions with no social smile or reciprocating facial expressions and was not babbling. She had inconsistent visual tracking and poor visual fixation on people and objects. The clinical treatment plan was focused on DOC, rather than spasticity, as this was the most significant impairment for this patient. Amantadine has been proven to be well tolerated and safe to use in the pediatric population and was chosen for this patient for its efficacy in the treatment of DOC [12,13]. Patient began Amantadine 1 week after initia visit at dose of 3.75 mg/kg/day divided into two doses. At 3 weeks after starting amantadine, she demonstrated improvements across several domains and mother reported that she began seeing positive changes within 2 weeks of starting the medication. On dynamic evaluation, she was able to sit independently for 5 minutes once placed, she had increased purposeful movements of right leg, and right arm movements were stimulated with tactile input to arm. Her level of alertness and arousal was significantly improved with social smile and engagement in interactive play activities. She had improved visual fixation and was able to consistently track across midline. Daily dose was increased to 5 mg/kg/day divided into two doses (Table 2). At each subsequent follow up visit, she demonstrated continued improvements. Two months after starting amantadine, she was able to roll independently in both directions, reach beyond base of support in sitting (once placed), demonstrate more active right arm & leg movement, and had increased social interaction and vocalizations. Three months after starting amantadine, she began to stand at surface and was able to sit for up to 20 minutes after placed. Four months after starting amantadine, she was able to independently bring self to sitting from supine, maintain standing against a wall for support and demonstrated improved play skills with toys. Six months after starting medication, she was able to bring self to quadruped position and move forward two paces, take steps in a baby walker (both forward and backward), used her right arm purposefully in gross movement patterns and began to imitate sounds.

Twelve months after starting medication, she began to pull to stand at surface, was attempting to cruise, scooted in sitting position for mobility, was speaking 5-7 words and continued to use right arm more. At this time, it was noted that her spasticity had resolved on the left side and was then only present in right arm (MAS 1), and leg (MAS 1+). A slow weaning plan was initiated for amantadine over a 12-week period with close monitoring for any regression of skills. At follow up visit 9 weeks into medication weaning, she had begun crawling in quadruped, had improved quality of pull to stand and was using right arm more functionally. She had not demonstrated any signs of regression.

Table 1: Imaging results.

Initial Brain CT Scan	Initial Brain MRI
· Focal left parenchymal & parietal hemorrhage · Mild midline shift · Low attenuation · Diffuse loss of grey-white differentiation · Subdural hemorrhage	· Subdural hemorrhagic product overlying posterior and lateral left cerebral hemisphere · Parenchymal hemorrhage in left parietal lobe · Subtle ischemia

Abbreviations: CT: computed tomography; MRI: magnetic resonance imaging

Table 2: Amantadine dosing.

Dose	Duration of Dose
3.75 mg/kg/day divided BID (TDD 30mg)	4 weeks
5 mg/kg/day divided BID (TDD 40mg)	19 months

Abbreviations: TDD: total daily dose

One month after completion of wean, she was taking steps with left hand held, able to push a toy shopping cart throughout the home, could stand independently for short periods and was speaking up to 10 words. She took amantadine for a total of 16 months and there were no reported side effects or complications from the medication throughout this period, nor did she have changes in any of her other medications or therapies during this time. She has remained off of amantadine without any regression and continues to make great progress. She is now four years old and is walking independently, is able to run and jump, is speaking in 4-5 word sentences, and has functional right hand skills with mild spasticity in right arm and right leg (Table 3).

DISCUSSION

Research has shown poor outcomes following pediatric TBI associated with young age groups (under three years old) and severity of injury [14,15]. Infancy is a period of rapid brain development and it is believed that the disruption of these processes following a brain injury may contribute to more severe adverse outcomes in this age group [16]. The patient in this case presented as very high risk for poor outcomes due to both her young age at time of injury and high level of severity of her brain injury. At the point when she was started on amantadine, she had shown minimal recovery from initial injury over the intervening six months. The US Food and Drug Administration approved amantadine in 1976 as an antiviral drug to treat influenza A in children older than one year of age, however it is no longer recommended for this indication in the pediatric population and is primarily used for the treatment of DOC in the TBI population [17,18]. There is a significant body of evidence supporting the use of amantadine to facilitate brain recovery in adults with TBI, but there is a lack of evidence to support the use of this medication in the pediatric population, particularly in infants. The small body of research of amantadine in the pediatric population has thus far consistently shown it to be well tolerated and a safe and effective medication with low side effect profile; however studies are limited in sample size and age of study participants are typically 6 years or older, with medication started in the acute phase of recovery [7,9,12,13,19]. The onset of therapeutic action of amantadine is relatively quick (within 4 days at each dose) which makes titration and monitoring simple. If toxicity or negative side effects develop, it is readily reversible when drug is weaned or withdrawn [20-22].

This case provides a unique perspective in using amantadine in the treatment of an infant with history of AHT, resulting in a severe TBI, due to the patient's young age at time of injury (3.5 months) as well as the initiation of treatment outside of the acute phase of recovery (6 months after injury). Studies are still lacking strong evidence to provide guideline for optimal times to initiate treatment with amantadine, whether it is best to

Table 3: Improvement of motor skills, social interaction and speech with amantadine.

Post Amantadine	Age (months)	Motor	Social Interaction	Speech
Baseline	10	No rolling No sitting No active right arm/leg movement	Minimal interest in toys Decreased alertness Poor visual tracking	Not babbling
Amantadine 3.75 mg/kg/day				
3 Weeks	11	Able to maintain sitting for short period R leg-Purposeful movement R arm-Response to tactile stimulation	Improve alertness Social smile Consistent visual tracking & fixation	Some babbling
Amantadine 5 mg/kg/day				
2 Months	13	Roll over: to both sides Reach beyond base of support in sitting More active right arm & leg movement	Increased social interaction "Demands" attention	Increased babbling
4 Months	15	Brings self to sit Able to sit for 20 minutes after placed Maintains standing against wall	Improve play skills with toys	Babbling
7 Months	18	Takes steps in baby walker Gets into quadruped Purposeful gross movement of right arm Uses primitive grasping patterns	Engages in reciprocal play	Imitating sounds & words
13.75 Months	24	Pulling to stand Cruising along surface More accurate right arm movements		Speaking 5-7 words in 2 languages
Amantadine taper started: carried out slowly over 12 weeks				
16 Month	26	Crawling in quadruped Functional grasping with right hand		Growing spoken vocabulary
After completion of amantadine				
	31	Walking with left hand held Walks pushing rolling toy Can stand independently for few seconds	Very social & playful	Speaking 10 words
	35	Walking independently using right hinged AFO Uses right arm as support		Putting 2-3 words together
Current function	48	Walking independently Able to run and jump Mild right sided spasticity Speaking in 4-5 word sentences		

start in the acute phase in inpatient rehabilitation or if there is indication to initiate these medications after discharge. Studies of the use of amantadine for children with developmental disorders, including autism spectrum disorder and attention deficit hyperactivity disorder, showed favorable or statistically significant improvement in attention, autistic behaviors, and/or depression and anxiety [19,23]. The results of these studies indicate that treatment with amantadine can be initiated for specific neurological deficits rather than focused on initiation of treatment within a certain time period following brain injury.

Additionally, there is not clear evidence to support the optimal length of time to continue the course of treatment with amantadine to achieve optimal outcomes and without risking regression of skills on discontinuation of medication. We were able to see global improvement within 2 weeks after starting the medication with the patient's mother reporting that the she was "more demanding" as one of the first indicators of improvement. This change reflected the patient's increase in arousal and alertness and was quickly followed by improvement in gross motor skills and mobility, increased awareness of and use of her right side, and improvement in spasticity. The amantadine was slowly weaned after 14 months at which time she had shown continuous progress across all domains of development and she did not show any signs of regression after the medication had been discontinued.

Given this patient's young age at the time of treatment, one can argue that her recovery could be due to natural recovery and brain plasticity, despite the known risk of poorer outcomes in young children with severe brain injury. This patient made minimal progress in her cognitive and motor function over 6.5 months between the time of injury to initial presentation at our clinic and did not begin to show significant recovery until amantadine was started. Therefore it is believed that amantadine played a significant role in her recovery. Future research should focus on treatment with amantadine in both the acute and chronic stages of recovery in TBI and DOC in order to establish guidelines for safe dosing of the medication in all pediatric age ranges. Additionally, well-designed studies are needed to determine the optimal timing to initiate treatment with amantadine and duration of treatment to achieve optimal outcomes.

This case supports the use of amantadine in infants, even in cases of chronic brain injury and prolonged DOC, to bring meaningful change to cognitive and motor function. It is still unclear at what point amantadine can be safely discontinued without regression of skills, but in this case, the patient took amantadine for over one year and was safely weaned off medication without signs of regression while continuing to demonstrate progress. Further studies are needed to provide additional evidence on the efficacy of amantadine in children with TBI, including younger ages.

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Cite this article

Newell A, Alfonso E, Kim H (2020) Amantadine Use in an Infant with Abusive Head Trauma: A Case Report. Ann Pediatr Child Health 8(4): 1186.